Brain Stimulation 6 (2013) 644–648

Contents lists available at SciVerse ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Articles

Comparing Cortical Plasticity Induced by Conventional and High-Definition 4 × 1 Ring tDCS: A Neurophysiological Study

Hsiao-I. Kuo [a], Marom Bikson [b], Abhishek Datta [b], Preet Minhas [b], Walter Paulus [a], Min-Fang Kuo [a,1], Michael A. Nitsche [a,*,1]

[a] Department of Clinical Neurophysiology, Georg-August-University Göttingen, Göttingen, Germany
[b] Department of Biomedical Engineering, The City College of the City University of New York, New York, NY, USA

ARTICLE INFO

Article history:
Received 19 April 2012
Received in revised form
24 September 2012
Accepted 24 September 2012
Available online 11 November 2012

Keywords:
Transcranial direct current stimulation
High definition tDCS
Human
Motor cortex
Plasticity

ABSTRACT

Background: Transcranial direct current stimulation (tDCS) induces long-lasting NMDA receptor-dependent cortical plasticity via persistent subthreshold polarization of neuronal membranes. Conventional bipolar tDCS is applied with two large (35 cm^2) rectangular electrodes, resulting in directional modulation of neuronal excitability. Recently a newly designed 4 × 1 high-definition (HD) tDCS protocol was proposed for more focal stimulation according to the results of computational modeling. HD tDCS utilizes small disc electrodes deployed in 4 × 1 ring configuration whereby the physiological effects of the induced electric field are thought to be grossly constrained to the cortical area circumscribed by the ring.
Objective: We aim to compare the physiological effects of both tDCS electrode arrangements on motor cortex excitability.
Methods: tDCS was applied with 2 mA for 10 min. Fourteen healthy subjects participated, and motor cortex excitability was monitored by transcranial magnetic stimulation (TMS) before and after tDCS.
Results: Excitability enhancement following anodal and a respective reduction after cathodal stimulation occurred in both, conventional and HD tDCS. However, the plastic changes showed a more delayed peak at 30 min and longer lasting after-effects for more than 2 h after HD tDCS for both polarities, as compared to conventional tDCS.
Conclusion: The results show that this new electrode arrangement is efficient for the induction of neuroplasticity in the primary motor cortex. The pattern of aftereffects might be compatible with the concept of GABA-mediated surround inhibition, which should be explored in future studies directly.

Introduction

Neuroplasticity is associated with cognitive functions including learning and memory formation, as well as the recovery process following brain damage. Transcranial direct current stimulation (tDCS) induces cortical plasticity non-invasively via subthreshold neuronal membrane polarization with constant weak direct currents [1–3]. Pharmacological experiments revealed the NMDA receptor and calcium-dependency of tDCS-induced plasticity [4–6]. The direction of tDCS-induced plastic changes depends on stimulation polarity – anodal stimulation conventionally results in excitability enhancement, while cathodal tDCS reduces it [1–3]. tDCS has been applied in the last years in a broad spectrum of experiments, ranging from basic research to clinical application conditions involving physiological and pathological alteration of cortical plasticity, and has been shown to enhance cognitive functions and to improve neurological impairment [4–6].

Current flow direction and amplitude and electrode montage are the main factors determining the efficacy of tDCS, which is usually applied with an intensity of 260 μA–2 mA and rectangular electrodes sized 16–35 cm^2 placed in a bipolar cortical montage (e.g. motor cortex – contralateral supraorbital montage for the stimulation of the primary motor cortex) [4]. Stimulation with these conventional parameters modulates cortical activity in a relatively larger area than that covered by the target electrode (i.e. motor cortex electrode for motor cortex stimulation), as demonstrated in neuroimaging studies [7]. Moreover, modeling studies suggest that the largest cortical current density might not occur directly under the target electrode in these conventional stimulation

* Corresponding author. Tel.: +49 551399571; fax: +49 551398621.
E-mail address: mnitsch1@gwdg.de (M.A. Nitsche).
[1] These authors contributed equally.

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http://dx.doi.org/10.1016/j.brs.2012.09.010

protocols [8,9]. However irrespectively of the effects of conventional tDCS on cortical excitability it will always be desirable to enhance or optimize stimulation focality.

Diminished electrode size has been shown to reduce affected cortical area size therefore increase focality [10]. In this study the current intensity was reduced according to size when compared with the standard size of 35 cm^2. Using smaller electrodes with gel-based designs, so-called "High-Definition" electrodes (gel-skin contact area: $\sim 25 \pm 2.5$ mm^2 with a plastic electrode holder), it allows tolerated stimulation of currents of up to 2 mA [11]. Deploying these electrodes in a 4×1 ring electrode configuration was predicted to focalize stimulation according to the finite element model analysis (FEM) based on high-resolution magnetic resonance imaging (MRI) [8,12]. The "4×1 HD tDCS" implements a concentric-ring electrode configuration with the active center electrode placed above the target area, which is surrounded by four return electrodes. According to modeling studies, this electrode configuration results in maximal electric field (EF) strength under the target electrode with brain current flow constrained by the 4×1 ring radius (for example 3.5 cm defined by the distance between active and each return electrode), and thus more spatially restricted electric field, as compared to the conventional electrode placement [8,12].

In these computational studies, EF magnitude was assumed to correlate with modulation of cortical excitability and activity. However, direct neurophysiological evidence for the efficacy of HD-tDCS is still lacking so far. In the present study, we compare motor cortical plasticity induced by both, conventional and HD tDCS, in healthy humans to explore the physiological effects of both stimulation designs. The results might serve as basis for the future application of specific tDCS protocols in both basic and clinical tDCS studies, where different stimulation focality is required.

Methods

Subjects

Fourteen healthy subjects participated in the experiment (6 men, 8 women, age 25.29 ± 3.2 (SD) years). All gave written informed consent. The investigation was approved by the ethics committee of the University of Goettingen and the experiments conform to the Declaration of Helsinki.

Transcranial direct current stimulation of the motor cortex

tDCS was administered with a current strength of 2 mA for 10 min (both for anodal or cathodal tDCS) by a battery-driven constant current stimulator (NeuroConn GmbH, Ilmenau, Germany). Two types of electrode configuration were applied:

1. Conventional rectangular sponge pad: we used a pair of saline-soaked surface sponge electrodes (active: 7×5 cm^2; return: 10×10 cm^2). The active electrode was positioned over the motor cortex representational area of the right abductor digiti minimi (ADM) muscle, and the return electrode was placed above the right supraorbital area. The larger return electrode was chosen to reduce the possible sensation and modulatory effect on the non-targeted brain area, as we have previously shown that this montage results in identical plastic effects at the stimulation site, as compared to the conventional protocols with two 35 cm^2 electrodes, while no effects were observed at the reference site [10].
2. 4×1 ring: The central active electrode was placed above the representational area of the right ADM muscle (coinciding with the center of the active pad used for regular-pad stimulation) and surrounded by four return electrodes (each at a ring center to ring center distance of 3.5 cm from the active electrode) which were connected to a four-to-one wire adaptor for the DC stimulator. Altogether 5 sintered Ag/AgCl ring electrodes (outer radius: 12 mm, inner radius: 6 mm) were stabilized with plastic holders filled with EEG conducting gel (H + H Medical Devices, Germany and with gel-skin contact area $\sim 25 \pm 2.5$ mm^2). Since the sensation to HD tDCS could differ in electrode and gel type [11], here we applied the suggested Ag/AgCl sintered ring electrodes [11], and the conducting gel for less skin sensation as reported by the subjects. A finite-element-methods (FEM) model of brain current flow in both electrode configurations is shown in Fig. 1.

Monitoring of motor cortical excitability

Single pulse TMS-elicited motor-evoked potentials (MEPs), of which the amplitudes served as an index of cortico-spinal excitability [13], were recorded to monitor tDCS-generated excitability changes of the primary motor cortex. Single-pulse TMS was conducted by a Magstim 200 magnetic stimulator (Magstim Company, Whiteland, Dyfed, UK) with a figure-of-eight magnetic coil (diameter of one winding = 70 mm, peak magnetic field = 2.2 T). The coil was held tangentially to the skull, with the handle pointing backwards and laterally at an angle of 45° from midline, inducing a posterior–anterior current flow direction in the motor cortex. The optimal position was defined as the site where stimulation resulted consistently in the largest MEPs. Surface EMG was recorded from the right ADM with Ag–AgCl electrodes in a belly-tendon montage. The signals were filtered with a low-pass filter of 2.0 kHz, then digitized at an analog-to-digital rate of 5 kHz and further relayed into a laboratory computer using the Signal software and CED 1401 hardware (Cambridge Electronic Design, Cambridge, UK). The intensity was adjusted to elicit MEPs of about 1 mV peak-to-peak amplitude on average at baseline determination before tDCS and was kept constant for the post-stimulation assessment.

Experimental procedures

The experiment was conducted in a complete crossover design. The order of different tDCS conditions was randomized. Each subject received 4 sessions of stimulation (one session per tDCS polarity, and electrode type). Between each session, a free interval of at least 1 week was obligatory. The experimental course was as follows: the subjects were seated in a reclining chair. First, TMS was applied over the left motor cortical representational area of the right ADM where it produced consistently the largest MEPs in the resting muscle (optimal site). The intensity of the TMS stimulus was adjusted to elicit MEPs with a peak-to-peak amplitude of on average 1 mV at baseline. Then tDCS was performed. After the end of tDCS, in the first minute, afterward for up to half an hour every fifth minute and up to 2 h every 30th min 20 MEPs were recorded to cover the time course of excitability changes. For HD tDCS, we performed an additional MEP measurement 6 hours after tDCS in 11 subjects, to probe the duration of the elicited cortical plasticity, because MEPs had not returned to baseline values 2 h after HD tDCS.

Calculations and statistics

The individual means of MEP amplitudes were calculated for both pre-stimulation baseline and the post-tDCS time points. The post-stimulation MEPs were normalized to baseline and are given as post-tDCS/baseline ratios. All results are shown as mean and

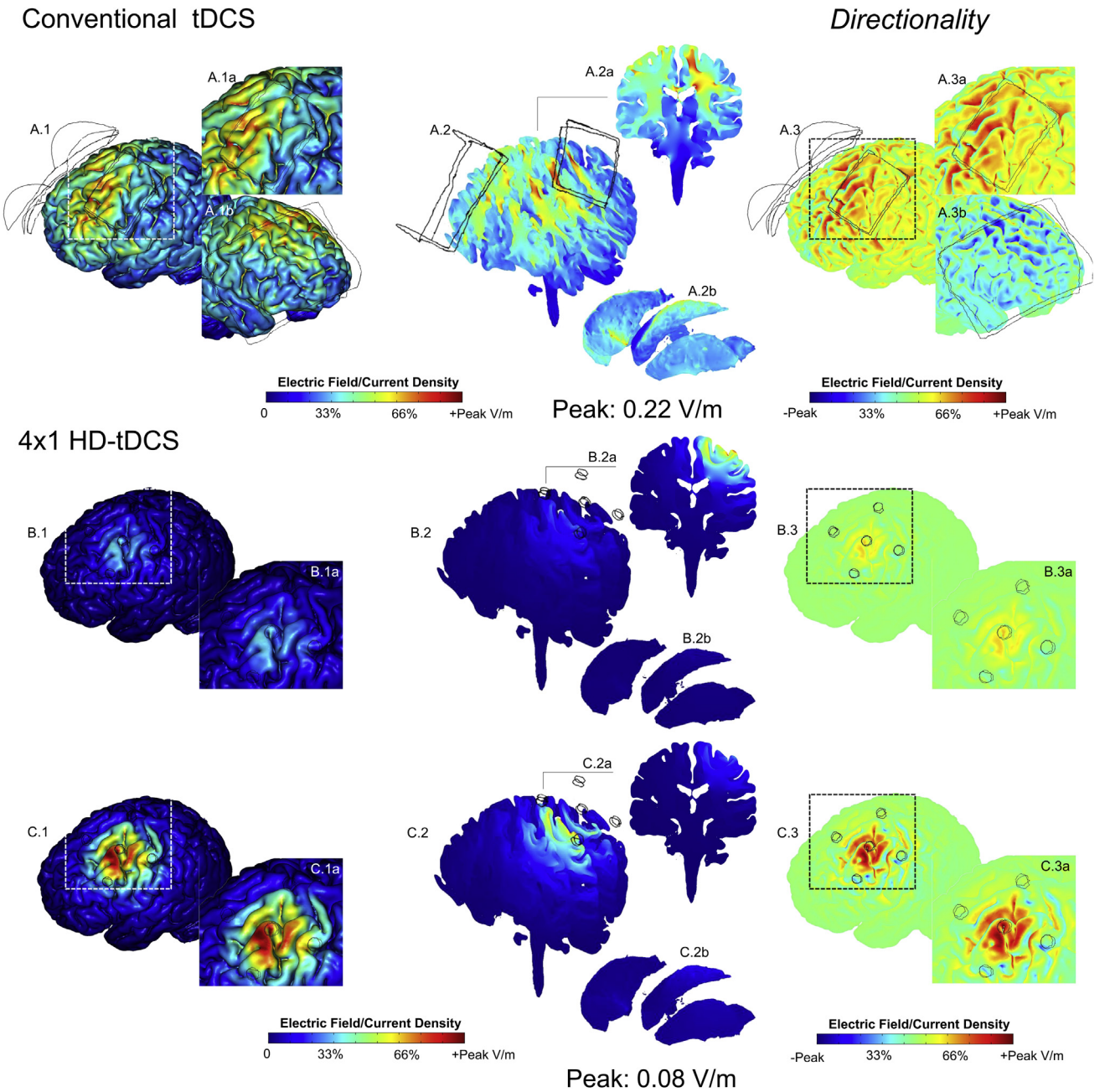

Figure 1. FEM model of brain current flow during conventional and 4×1 HD-tDCS. Cortical surface (first column), cortical cross-section (second column), and deep brain structure (second column inset) plots illustrate electric field magnitude (directionless. Blue = Zero electric field, Red=Peak magnitude). In the right column only the electric field normal to the cortical surface is shown (Blue = peak outward current, Green = Zero normal current, Red = peak inward current). **Top row**: Consistent with previous models, conventional tDCS produces diffuse current flow with local clustering. Current appears dominantly inward near the M1 anode. Some current also penetrates to deep brain structures. **Middle row**: 4×1 HD-tDCS induced current flow plotted on the same scale as conventional tDCS. Using the same total applied current (1 mA), the 4×1 configuration produces brain current flow restricted within the ring as, with 3.5 cm separation, a peak brain electric field ~40% of peak electric field induced across the brain using conventional stimulation and ~75% of the peak electric field induced in M1 by conventional stimulation. **Bottom row**: HD-tDCS induced current flow plotted on relative to its own peak electric field. Current is largely restricted to superficial structures.

standard error of the mean (SEM). For the resulting data, a repeated measurement ANOVA was calculated with the repeated measure factors electrode configurations, tDCS polarity and time points, and the dependent variable MEP size normalized to baseline. Conditional on significant results of the ANOVA, Student's *t* tests (paired samples, two-tailed) were performed to test whether the values of the MEP size differed for the time-points after stimulation vs. baseline, and between the electrode types at each time point after tDCS. Comparisons of baseline values were performed to exclude a priori differences. A P value of <0.05 was considered significant for all statistical analyses. The Mauchly test of sphericity was checked and the Greenhouse-Geisser correction was performed, when appropriate.

Results

Some subjects reported a tingling sensation during tDCS with both polarities and electrode configurations. Eight out of

Table 1
Baseline MEP amplitudes and TMS intensities of each stimulation type.

Stimulation type	Baseline MEP (mV)	TMS intensity (% MSO)
Conventional tDCS anodal	1.023 ± 0.036	54.1 ± 2.4
Conventional tDCS cathodal	0.939 ± 0.038	54.5 ± 2.7
4 × 1 ring tDCS anodal	0.990 ± 0.028	55.6 ± 2.7
4 × 1 ring tDCS cathodal	1.040 ± 0.031	53.9 ± 2.7

Baseline MEPs are 1 mV on average in all stimulation types and did not differ between conditions (paired *t*-test, $P > 0.05$). TMS intensities applied in each condition also showed no significant differences. Values are presented as mean ± standard errors. MSO: maximum stimulator output.

14 subjects mentioned less tingling with ring electrodes compared to the conventional sponge pads. No further adverse effects were reported.

Baseline MEP amplitudes and TMS intensities did not differ between stimulation conditions (see Table 1). The ANOVA revealed significant main effects of electrode configurations ($F = 593.646$, d.f. $= 1$, $P < 0.001$) and time course ($F = 8.369$, d.f. $= 10$, $P < 0.001$), significant interactions of tDCS polarity x time course ($F = 13.033$, d.f. $= 10$, $P < 0.001$), electrode configuration × time course ($F = 77.149$, d.f. $= 10$, $P < 0.001$), and tDCS polarity × electrode configurations × time course ($F = 36.406$, d.f. $= 10$, $P < 0.001$). For anodal stimulation, conventional tDCS induced excitatory plasticity which returned to baseline gradually until 120 min after stimulation, while HD tDCS elicited increasing excitability changes with a delayed peak at 30 min and then a decay to baseline by 6 h post tDCS, as revealed by the post-hoc *t*-tests. However, it should be noted that the excitability changes induced by HD tDCS could have returned to baseline earlier, since there was no additional measurement between 2 and 6 hours post HD tDCS. A similar plasticity evolvement was observed after cathodal tDCS for both electrode configurations. Here cortical excitability showed an initial reduction, which gradually increased up to a maximum about 30 min post tDCS in both conditions. HD tDCS generated a steeper excitability decrement, and a prolonged excitability reduction, as compared to conventional tDCS (Fig. 2).

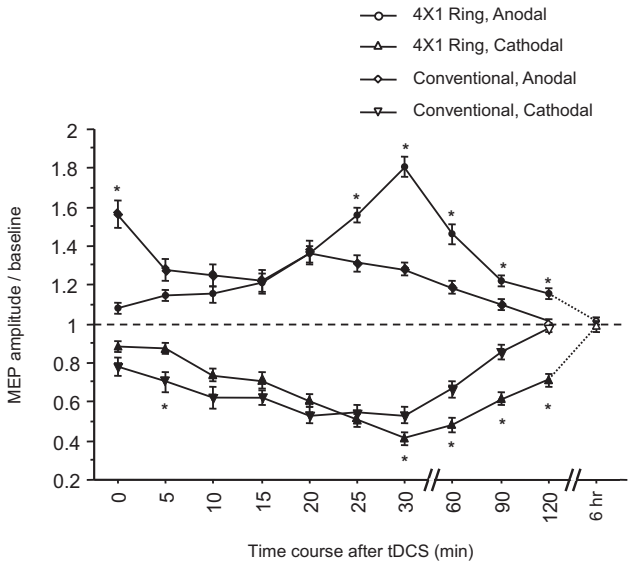

Figure 2. Neuroplasticity induced by conventional rectangular and HD tDCS protocols. Anodal tDCS with both, conventional and ring configurations, induced excitatory aftereffects. The excitability alterations obtained by the conventional protocol vanished 120 min post tDCS, while in the HD stimulation protocol excitatory after-effects were steadily increased, peaked at 30 min post stimulation, and returned to baseline more than 2 hours post stimulation. A similar trend was observed for the cathodal tDCS-induced excitability-diminishing plasticity with both stimulation protocols. The excitability diminution elicited by HD stimulation was most prominent 30 min after tDCS and also prolonged, as compared to conventional tDCS. Filled symbols: significant deviation from baseline ($P \leq 0.05$). Error bar: standard error of the mean (SEM). Asterisk: significant difference between conventional and HD tDCS protocols for anodal/cathodal tDCS.

Discussion

HD tDCS was recently developed on the basis of computational modeling studies to enhance the focality of tDCS [8,12]. So far, the functional effects of HD tDCS were only tested in one pilot study on pain perception, where HD tDCS over the primary motor cortex appeared to be well tolerated and significantly increased pain threshold [14], similar to the effects of conventional tDCS [15,16]. Nevertheless, direct physiological evidence for the plasticity-inducing properties of this new stimulation protocol as revealed by MEP protocols was missing so far. The results of the present study show that bi-directional plasticity can be induced by HD tDCS, and that the principal effects fit those of conventional tDCS protocols. Anodal stimulation elicited excitatory after-effects and cathodal tDCS induced a reduction of motor cortex excitability. However, the time course of the respective excitability alterations differed between conventional and HD tDCS. After conventional tDCS, cortico-spinal excitability was increased or decreased, according to the stimulation polarity, to a larger extent immediately after tDCS and then gradually returned to baseline level. In contrast, plasticity induced by HD tDCS reached the peak of the respective excitability alteration at about 30 min after stimulation. Moreover, the after-effects lasted at least 30 min longer than those obtained with conventional tDCS.

These results demonstrate that HD tDCS induces stimulation polarity-dependent plasticity in the motor cortex of healthy humans. Interestingly, the specific pattern of excitability alterations differs gradually between conventional and HD tDCS. The reasons for these differences are unknown at present. They could be due to the variant EF distribution as shown in computational simulations, where HD tDCS generates a more focused EF field, which has its maximum under the stimulation electrode, as compared to conventional tDCS, which results in a less focal electrical field [8]. Due to the distinctive nature of current direction and EF distribution between the two tDCS configurations applied in the present study, different groups of neurons (for example cortical interneurons or corticospinal neurons) or afferent axons may have been differently modulated depending on their properties and susceptibility to the electrical stimulation [17]. These presumed physiological differences should be explored to a larger extent in future studies. Moreover, a more systemic investigation to compare the effects of different stimulation intensities, durations, and electrode configurations on induced neuroplasticity will be important topic for further experiments.

Testing for focality of the effects of both protocols was beyond the scope of the present study. Indirect physiological evidence for a more focal effect of the ring electrode configuration other than modeling approaches comes from the results of another study, where diminished stimulation electrode size with an otherwise conventional tDCS protocol resulted in more focused physiological effects [10]. The presumed increased focality of 4 × 1 HD tDCS should however be tested directly in future experiments.

The effect of 4 × 1 tDCS could also be explained by the center-surround interaction principles, which are probably mediated by GABAergic mechanisms [18]. GABAergic mechanisms in conjuction with tDCS have been studied previously, where both for short and for longer stimulation protocols similar pictures arose for andol tDCS after-effects under loracepam, namely a delayed onset of and a prolonged decline of the respective excitability enhancement [19].

It would therefore be interesting to explore the mechanisms of 4 × 1 HD tDCS by testing GABA-related intracortical connections with paired-pulse TMS protocols or pharmacologic modulation of the GABAergic system.

Taken together, the results of our experiment demonstrate the neurophysiological efficacy of HD tDCS on motor cortex plasticity. 4 × 1 HD tDCS, as well as other HD deployments, may offer the opportunity to induce plasticity more focally than conventional tDCS protocols, which might be of relevance for studies aiming to explore the contribution of specific cortical areas to cognition and behavior, but also for clinical applications.

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