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Differential effects of anodal and dual tDCS on sensorimotor functions in chronic hemiparetic stroke patients

Toni Muffel [a, b, c, d, *], Pei-Cheng Shih [a], Benjamin Kalloch [a, e], Vadim Nikulin [a, f, g], Arno Villringer [a, b, c, d], Bernhard Sehm [a, b, h]

[a] Neuroplasticity & Motor Recovery Group, Department of Neurology, Max Planck Institute for Human Cognitive & Brain Sciences, Leipzig, Germany
[b] Day Clinic for Cognitive Neurology, University Hospital at the University of Leipzig, Leipzig, Germany
[c] MindBrainBody Institute, Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Berlin, Germany
[d] Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin, Berlin, Germany
[e] Faculty of Computer Science and Media, Leipzig University of Applied Sciences, Leipzig, Germany
[f] Neurophysics Group, Department of Neurology, Campus Benjamin Franklin, Charité-Universitätsmedizin Berlin, Berlin, Germany
[g] Bernstein Center for Computational Neuroscience, Berlin, Germany
[h] Department of Neurology, University Hospital at the Martin Luther University of Halle-Wittenberg, Halle, Germany

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ABSTRACT

Background and purpose: Previous tDCS studies in chronic stroke patients reported highly inconsistent effects on sensorimotor functions. Underlying reasons could be the selection of different kinematic parameters across studies and for different tDCS setups. We reasoned that tDCS may not simply induce global changes in a beneficial-adverse dichotomy, but rather that different sensorimotor kinematics are differentially affected. Furthermore, the often-postulated higher efficacy of bilateral-dual (bi-tDCS) over unilateral-anodal (ua-tDCS) could not yet be demonstrated consistently either. We investigated the effects of both setups on a wider range of kinematic parameters from standardized robotic tasks in patients with chronic stroke.

Methods: Twenty-four patients with arm hemiparesis received tDCS (20min, 1 mA) concurrent to kinematic assessments in a sham-controlled, cross-over and double-blind clinical trial. Performance was measured on four sensorimotor tasks (reaching, proprioception, cooperative and independent bimanual coordination) from which 30 parameters were extracted. On the group-level, the patterns of changes relative to sham were assessed using paired-samples *t*-tests and classified as (1) performance increases, (2) decreases and (3) non-significant differences. Correlations between parametric change scores were calculated for each task to assess effects on the individual-level.

Results: Both setups induced complex effect patterns with varying proportions of performance increases and decreases. On the group-level, more increases were induced in the reaching and coordination tasks while proprioception and bimanual cooperation were overall negatively affected. Bi-tDCS induced more performance increases and less decreases compared to ua-tDCS. Changes across parameters occurred more homogeneously under bi-tDCS than ua-tDCS, which induced a larger proportion of performance trade-offs.

Conclusions: Our data demonstrate profound tDCS effects on sensorimotor functions post-stroke, lending support for more pronounced and favorable effects of bi-tDCS compared to ua-tDCS. However, no uniformly beneficial pattern was identified. Instead, the modulations varied depending on the task and electrode setup, with increases in certain parameters occurring at the expense of decreases in others.

Abbreviations: bi-tDCS, bilateral-dual transcranial direct current stimulation; ua-tDCS, unilateral-anodal transcranial direct current stimulation; APM, Arm Position Matching task; CBC, cooperative bimanual coordination (Ball on Bar task); IBC, independent bimanual coordination (Object Hitting task); VGR, Visually Guided Reaching task.

* Corresponding author. Neuroplasticity & Motor Recovery Group, Max Planck Institute for Human Cognitive & Brain Sciences, Leipzig, Germany.
E-mail address: muffel@cbs.mpg.de (T. Muffel).

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1. Introduction

Stroke constitutes a leading cause of acquired disability in higher age [1] as the recovery of cognitive and motor functions remains incomplete for most patients [2], impairing their life quality [3]. It is, therefore, imperative to explore new avenues to improve rehabilitation after stroke.

Transcranial direct current stimulation (tDCS) is a technique that is safe to administer in patients [4] and is increasingly applied as neuromodulatory adjuvant to neurorehabilitation. Unilateral-anodal tDCS (ua-tDCS), aiming at the facilitation of the ipsilesional sensorimotor cortices, is the most extensively studied setup and has been shown to improve a variety of motor outcomes measures in stroke patients [5]. Similarly, unilateral-cathodal tDCS has been reported to effectively modulate performance by inhibiting overactive contralesional cortices [6]. Dual or bilateral tDCS (bi-tDCS) combines the facilitation of the ipsilesional cortices (anodal component) with the inhibition of the contralesional cortex (cathodal component) and has thereby been shown to induce stronger effects than either unilateral setup [7]. Other studies, however, did not demonstrate these canonical [8] performance modulations for either setup [9–11] and recent meta-analyses and systematic reviews [12–15] increasingly reveal heterogeneous and variable effects of tDCS on sensorimotor functions after stroke. One possible explanation could be that most previous studies only investigated effects on a limited set of movement parameters. Therefore, potential diverging effects on different aspects of (sensori)motor function may have been overlooked, particularly since most studies performed only between-group comparisons and thereby often fully neglected the individual-level at which large variability in responses occurs [8].

To overcome these issues, we here combine standardized robotic assessments of sensorimotor control with a double-blind, sham-controlled, cross-over experimental design to assess functional effects of tDCS in stroke patients with arm paresis. Focusing on the facilitation of the lesioned cortices, we use established protocols for ua-tDCS and bi-tDCS to assess setup-specific effects. Based on the evidence mentioned above [5,7], we hypothesized detectable performance changes in response to either tDCS setup with the aim to improve movement performance. Moreover, we expected overall behavioral improvements under both setups albeit with considerably larger proportions of functional improvements under bi-tDCS. By assessing multiple kinematic parameters simultaneously, we expected that not all parameters would be affected equally and hypothesized complex and interrelated patterns of either performance increases or decreases as well as unchanged parameters.

2. Methods

Data sets are available from the corresponding author upon reasonable request.

2.1. Patient sample

Patients were recruited from the Day Clinic for Cognitive Neurology at the University Hospital Leipzig. They were briefed about study procedures and intent and provided written informed consent in accordance with the Declaration of Helsinki. Twenty-four patients (16 males, mean age: 60.2 ± 12.4 years) with first stroke occurrence (13 right-affected) and mild to moderate upper extremity hemiparesis at least 6 months post-stroke were recruited. Fig. 3 provides a clinical characterization and lesion distributions; Fig. 4 displays individual sensorimotor deficits of the sample. Detailed information on patient recruitment and patient characteristics are provided in the Supplemental Material Section 1. The study was approved by the Ethics Committee of the University of Leipzig.

2.2. Experimental design and procedure

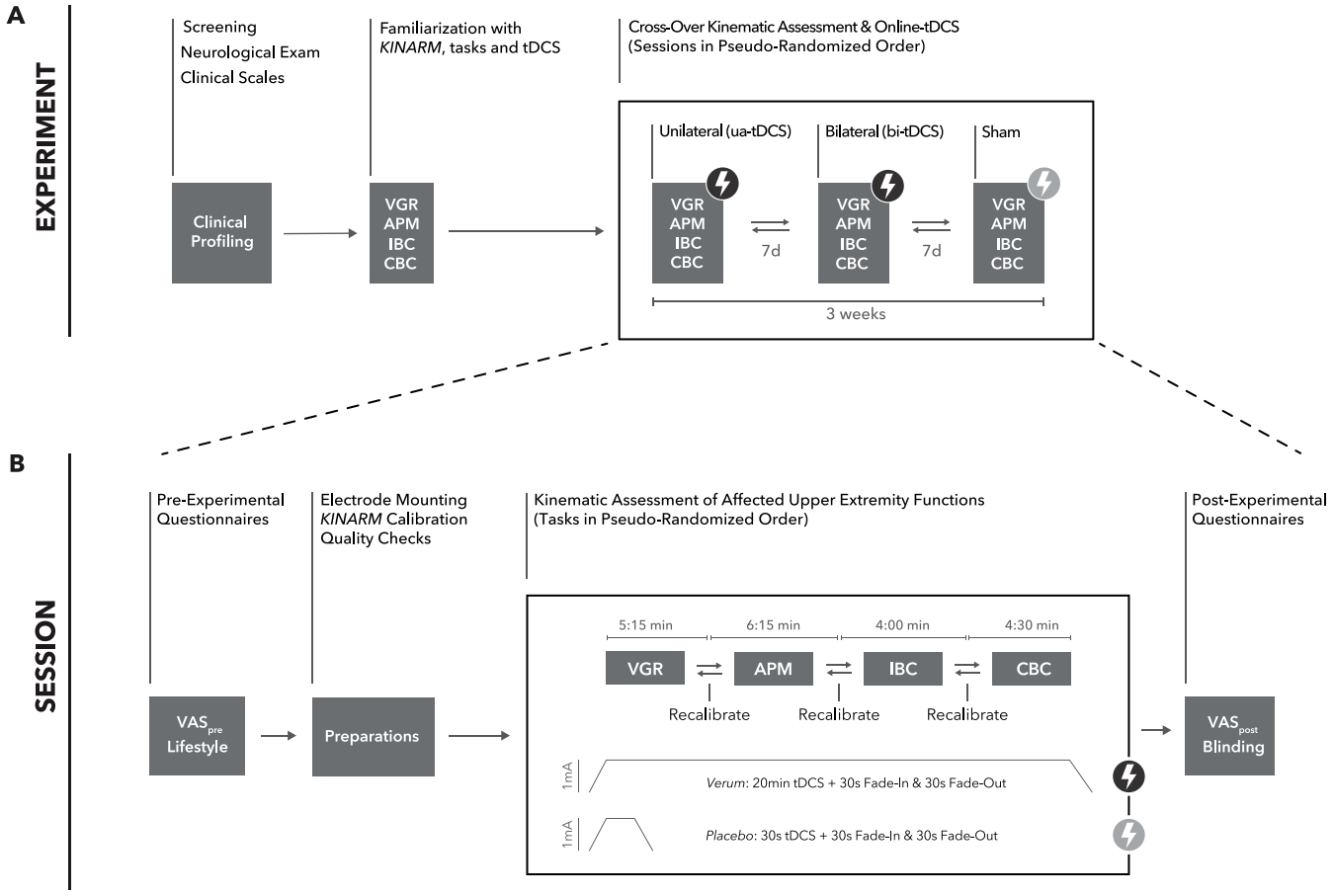
A double-blind, cross-over design was adopted. Overall experimental procedures are illustrated in Fig. 1. A. Patients underwent neurological examinations before enrolment, where standardized clinical scales (Fig. 3.A, Supplemental Table I) were acquired by experienced staff. Enrolled patients were familiarized with the experimental setup, equipment and tested all kinematic tasks prior to data collection. The effects of stimulation were assessed in three test sessions, each separated by at least one week to avoid carry-over effects of tDCS [16]. The experimental procedures and kinematic assessments were identical in each session apart from the applied tDCS setup (Fig. 1.B). The order of sessions (tDCS setups) and kinematic tasks was pseudo-randomized across patients: respective randomization lists were generated *a priori* in MATLAB 9.3. (R2017b, MathWorks, Inc., Natick, MA, USA) and patient IDs were filled successively when a new patient was enrolled. Neuroimaging data were acquired for half of the sample before and the other half after the behavioral assessments. All data collection was conducted by the same blinded experimenter. A second experimenter allocated patients to the randomization lists, supervised the stimulator during testing and assisted with preparations but did otherwise not interact with patients.

2.3. Kinematic assessments

All kinematic assessments were performed on a second-generation *KINARM* exoskeleton lab (BKIN Technologies, Canada, Fig. 1.C) using Dexterit-E 3.6.2 [17]. KINARM can initiate upper extremity movements and reliably record in-plane movements in high temporal and spatial resolution [18,19].

Sessions (Fig. 1.B) commenced with a questionnaire on life-style variables and visual analogue scales for attention, wakefulness and pain. After tDCS preparations, the exoskeleton was adjusted to fit individual limb segment lengths and the system was calibrated. Adjustment and calibration parameters were recorded to avoid a measurement bias between sessions (tolerance: ± 1 cm). Task instructions were repeated in a standardized way to maximize compliance. Four tasks (Fig. 1.D) were used for kinematic assessments: *Visually Guided Reaching* (VGR) to quantify movement planning and execution with different reaching movements of the affected arm [20]; *Arm Position Matching* (APM) to measure static limb position sense of the affected arm without visual feedback [21]; the *Object Hitting* to test independent bimanual coordination (IBC) and rapid motor decisions [22]; and *Ball on Bar* to assess cooperative bimanual coordination (CBC) [23].

This array of tasks was chosen to complementarily assess different sensorimotor functions that are likely to be prone to a modulatory intervention, such as tDCS, in a controlled and ecologically valid way. The VGR task is a simple motor task which represents a direct read-out of motor performance of the affected arm. It is well-controlled and ecologically valid for unimanual goal-directed reaching movements. The APM task captures proprioceptive perception, a function that is of paramount importance for both coordinated sensorimotor performance and learning. Moreover, proprioception is a pre-requisite for successful motor recovery after stroke [24] and could be a potential target function for tDCS-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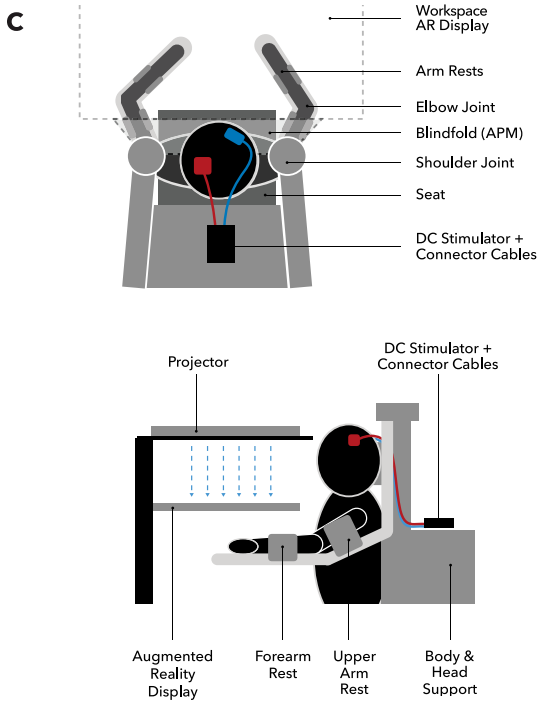
Screening
Neurological Exam
Clinical Scales
Familiarization with
KINARM, tasks and tDCS
Cross-Over Kinematic Assessment & Online-tDCS
(Sessions in Pseudo-Randomized Order)
Clinical Profiling
VGR
APM
IBC
CBC
Unilateral (ua-tDCS)
Bilateral (bi-tDCS)
Sham
7d
7d
3 weeks
B
SESSION
Pre-Experimental Questionnaires
Electrode Mounting
KINARM Calibration
Quality Checks
Kinematic Assessment of Affected Upper Extremity Functions
(Tasks in Pseudo-Randomized Order)
Post-Experimental Questionnaires
VAS pre Lifestyle
Preparations
5:15 min
6:15 min
4:00 min
4:30 min
VGR
APM
IBC
CBC
Recalibrate
Recalibrate
Recalibrate
VAS post Blinding
1mA
Verum: 20min tDCS + 30s Fade-In & 30s Fade-Out
1mA
Placebo: 30s tDCS + 30s Fade-In & 30s Fade-Out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AR Display
Arm Rests
Elbow Joint
Blindfold (APM)
Shoulder Joint
Seat
DC Stimulator +
Connector Cables
Projector
DC Stimulator +
Connector Cables
Augmented
Reality
Display
Forearm
Rest
Upper
Arm
Rest
Body &
Head
Support

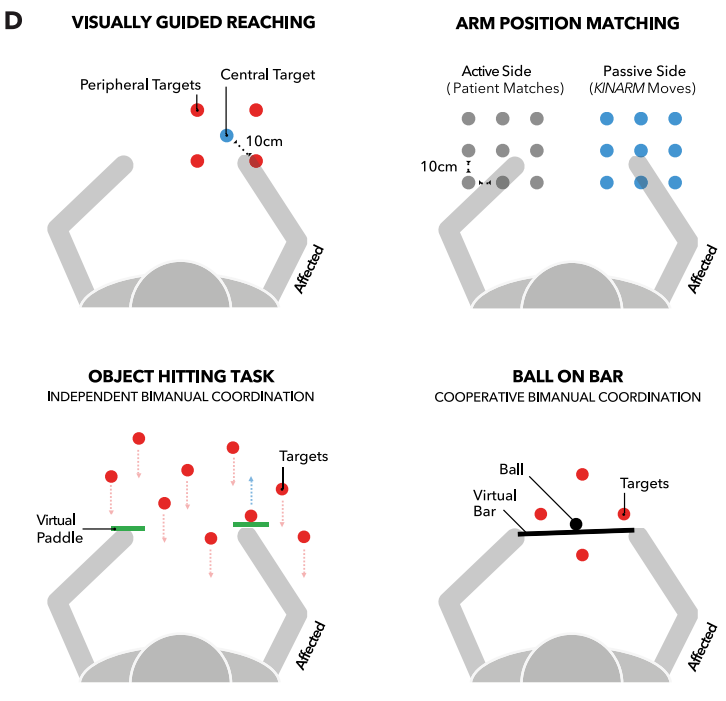

D
VISUALLY GUIDED REACHING
Peripheral Targets
Central Target
10cm
Affected
ARM POSITION MATCHING
Active Side
(Patient Matches)
Passive Side
(KINARM Moves)
10cm
Affected
OBJECT HITTING TASK
INDEPENDENT BIMANUAL COORDINATION
Targets
Virtual
Paddle
Affected
BALL ON BAR
COOPERATIVE BIMANUAL COORDINATION
Ball
Virtual
Bar
Targets
Affected

Fig. 1. Experimental Design and Kinematic Assessments. **A** Testing occurred on three days separated by one week in a pseudo-randomized, cross-over design. **B** The same standardized procedures were used for all three sessions, only tDCS setups changed in pseudo-randomized order. Visual analogue scales and lifestyle-related information were acquired before and after testing (Supplemental Material Section 2). **C** tDCS was applied concurrent to task execution in the *KINARM* robotic environment. The semi-translucent mirror between hands and projector served as augmented-reality interface to simultaneously display stimulus material and visual feedback of hand positions. **D** Workspaces and virtual stimulus material are specific to each task and positionally adjusted for each patient. Exemplary workspaces provided for a right-affected patient. Workspaces were flipped for left-affected patients. Abbreviations: *APM* = Arm Position Matching (proprioception), *CBC* = Cooperative Bimanual Coordination, *IBC* = Independent Bimanual Coordination, *VGR* = Visually Guided Reaching (unimanual).

supplemented therapies post-stroke. The bimanual tasks (IBC, CBC) were included as they investigate more complex aspects of sensorimotor control which are important components of a naturalistic motor repertoire. The two tasks are ecologically valid for coordinated bimanual everyday life tasks, such as carrying and navigating objects (e.g., a tray) or independently reacting to stimuli with both hands. The kinematic parameters obtained from all robotic tasks are well relatable to existing research on motor control [25].

Full details on all tasks are provided in Supplemental Material Section 3. Tasks were tested in allocated time windows and their order was pseudo-randomized across subjects (Fig. 1.B). To remove order effects on performance and to achieve distributed dosages of tDCS on all tasks across patients, the order of tasks was pseudo-randomized across patients and sessions. Stimulation durations should have been sufficient for all tasks as previous studies demonstrated online effects as early as 5 min into stimulation [26]. Sessions concluded with post-experimental ratings of attention, wakefulness and pain.

2.4. Transcranial direct current stimulation

Electrode setups, stimulation parameters and preparatory procedures were based on previously published protocols [5,16,27–30]. The anode was placed over the ipsilesional M1 hand area (C3 or C4) to modulate performance of the affected arm. The cathode was positioned over the contralesional forehead (Fp2 or Fp1, respectively) for ua-tDCS or the contralesional M1 hand area (C4 or C3, respectively) for bi-tDCS (Fig. 2). We used the conventional procedure for determining electrode positions based on the nasion-inion distance and inter-tragus distance [31] in accordance with the international 10–20 EEG coordinate system [32]. After scalp cleansing with alcoholic pads (B. Braun, Germany), square rubber electrodes (5×5 cm^2, $D_I = 0.04$ mA/cm^2, $Q_{total} = 0.048$C/cm) were mounted using Ten20 conductive electrode paste (Weaver and Company, USA) and 7 cm wide hook-and-loop fabric bands. 1 mA of unidirectional constant direct current was delivered using a DC Stimulator MR (NeuroConn, Ilmenau, Germany) for 20 min during ua-tDCS and bi-tDCS and for 30 s during sham. Current was linearly faded in and out for 30 s. To obtain a basic estimate of electrical field distributions based on the given stimulation parameters, a simulation of the prototypical electrical field patterns induced by both tDCS setups was performed in SimNIBS 2.1 [33] using the provided standard MNI head model (Fig. 2) and default electrical conductivity values (scalp: 0.465 S/m, bone: 0.01 S/m, cerebrospinal fluid cerebrosinalc: 1.654 S/m, grey matter: 0.275 S/m, white matter: 0.126 S/m, eyes:0.5 S/m). The electrodes were modeled with their power inlet and a gel layer between the scalp and electrodes. Electrode positioning was performed in SimNIBS as well by specifying the 10–20 coordinates of the electrodes as measured in the lab. Individual simulations incorporating individual head and lesion morphologies were not performed as those were beyond the focus of this paper.

To control the quality of the repeated measures design and to avoid potential confounders for tDCS effects, lifestyle variables like individual circadian rhythm, sleep, physical activity, substance consumption as well as head measurements, electrode resistances, blinding and changes in visual analogue scales for levels of attention, wakefulness and pain were acquired. Detailed descriptions and results are provided in Supplemental Material Section 2. In short, there were no significant differences regarding lifestyle variables, electrode placement parameters or levels of attention, wakefulness and pain – including their change within sessions – between tDCS setups. No tDCS side-effects were reported.

2.5. Data analysis

2.5.1. Preprocessing

To quantify the modulation of sensorimotor performance due to tDCS, session means across all trials were calculated for all kinematic parameters of each task using Dexterit-E. To comprehensively assess overall sensorimotor performance, all parameters that met the following criteria were to be included into statistical analysis: parameters were required to (i) provide information which was not otherwise covered by other parameters and (ii) changes in parameters were required to be identifiable as performance increases or decreases. Accordingly, a subset of 30 parameters across tasks was selected *a priori*. Justifications for the inclusion vs. exclusion of each parameter are provided in Supplemental Tables II – V. Detailed task and parameter descriptions along with preprocessing steps are provided in Supplemental Material Section 3.

We chose to include as many parameters as possible to not restrict our assessments to only select outcome parameters which, as often criticized as limitation to other publications, would only assess distinct aspects of sensorimotor control. Moreover, dimensionality reduction techniques (e.g., principal component analysis, as recently applied to the KINARM tasks by Wood et al. [34], or cluster analysis) were inapplicable due to the large disproportion between parameters and observations [35]. Parameter subgrouping, for instance, by the nature of parameters (e.g., temporal vs. spatial), their differential dependence on physiological systems (e.g., motor outputs, somatosensory input, visual processing, etc.) or functional meaning (e.g., speed vs. accuracy) could not always be performed fully unambiguously and was, therefore, disregarded.

Raw scores were corrected for the influence of covariates [36] by applying multiple linear regression before data analysis using age [37] and Fugl-Meyer-scores [38] as regressors in SPSS 20 (SPSS Inc., USA). A correction for handedness and sex was not performed as no interaction between both variables could be observed across kinematic parameters (Supplemental Material section 3.7). Resulting unstandardized parameter estimates were used for subsequent statistical analyses.

2.5.2. Statistical analysis

A two-tailed alpha-level of 5% was used for all inferential statistics.

2.5.3. t-Tests

To assess the setup-specific effect patterns, differences between the two setups and sham were calculated using paired *t*-tests. For each parameter, *t*-test results were classified as (1) performance

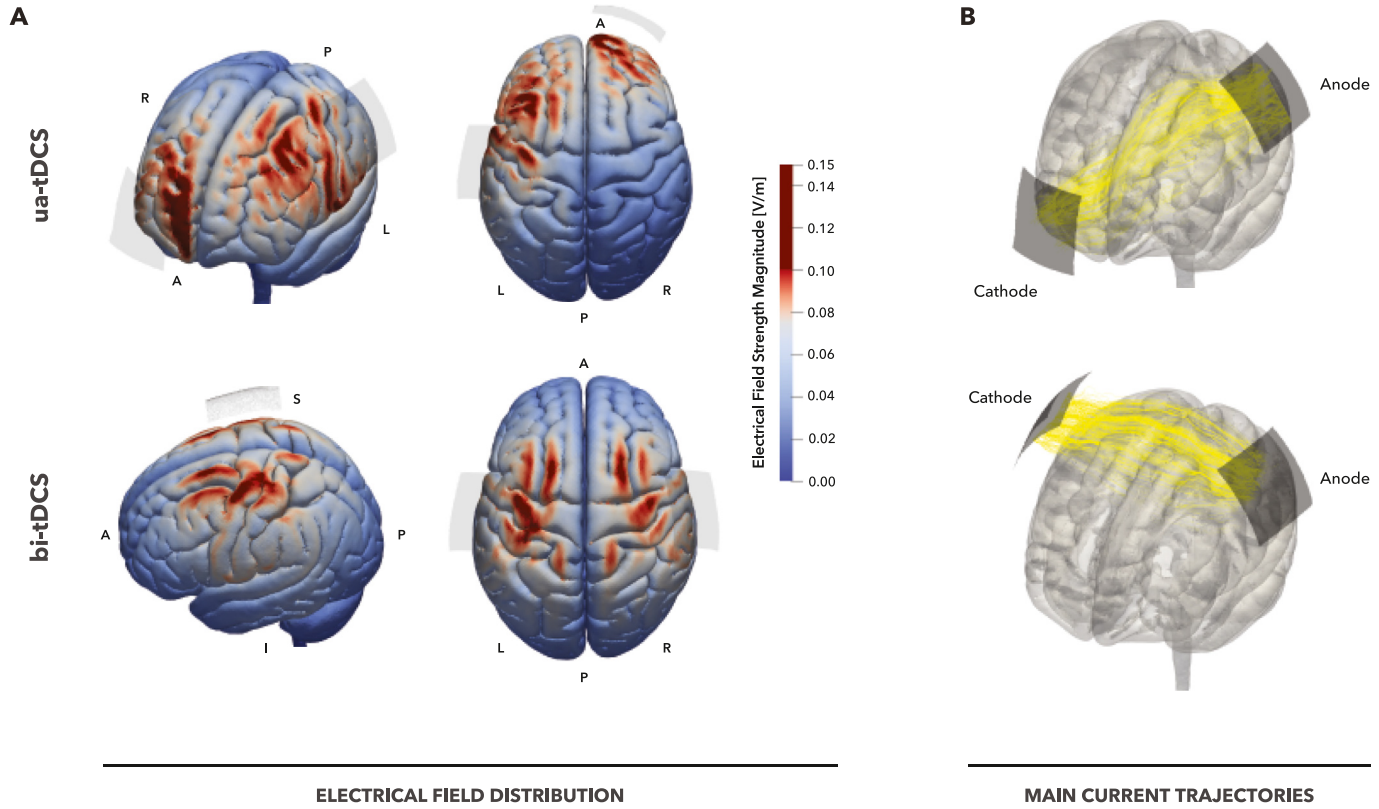


Fig. 2. tDCS Simulation and Electrode Setups. **A** Red areas indicate regions with higher field strengths. For the purpose of clearer visualization, field strengths above 0.1 V/m are capped to highlight brain regions with the highest intensities. **B** Major current trajectories (yellow) between the two electrodes (black) illustrate the principal orientation of current flow. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

increases, (2) decreases or (3) non-significant changes compared to sham. Frequencies for each category were counted task-wise and across all tasks. Permutation tests (5000 iterations) were performed to control for falsely positive statistics [39]. The permutations were synchronized across tests to account for possible collinearities between parameters. Refer to Supplemental Material Section 3 for parameter directionality interpretations, statistical assumption tests and permutation procedures. The ratios between performance increases and decreases under stimulation over the total amount of significant parameters was compared using Fisher's exact tests.

To assess a superiority between the two setups directly, paired *t*-tests were calculated for the performance under ua-tDCS vs. bi-tDCS analogously to the procedure described above. These differences do not account for baseline performance. As superior performance could either mean actual better performance or less detrimental performance, caution is warranted when interpreting these results.

2.5.4. Inter-parameter correlations

To further investigate the pattern of changes on the individual-level, relationships among changes between parameters were assessed task-wise. Change scores from sham to stimulation were calculated for ua-tDCS and bi-tDCS on each parameter using the formula [40] $\triangle\%_{stimulation}$ = (performance $_{sham}$ − performance $_{stimulation}$) / performance $_{sham}$ * 100 in SPSS. Change scores were correlated across all parameters for each task using Kendall's Tau. Resulting positive coefficients were considered *mutual performance increases* if most (>50% of cases) underlying change scores were $\triangle\% > 0$, and *mutual decreases* if most were $\triangle\% < 0$. As negative coefficients indicate that an increase in one parameter comes at the "cost" of decreases in another, those were considered inter-parametric *trade-offs* (Fig. 5.B).

3. Results

3.1. t-Tests

Overall, effects of bi-tDCS were more pronounced, as more parameters were significantly changed irrespective of change directionality (ua-tDCS: 60%, bi-tDCS: 70%), and more beneficial than ua-tDCS, as more performance increases (20% vs. 36.7%) and less decreases (40% vs. 33.3%) occurred (Fig. 5.A, Table 1 and Supplemental Table VI). While larger proportions of increases were observed in VGR and IBC, both setups predominantly induced decreases in APM and CBC. Four parameters were not significantly affected by either setup for which physiological or kinematic similarities, however, could not be established. The effect strength varied in a similar task- and setup-specific way and were on average larger for bi-tDCS ($d = 0.84 \pm 0.96$) than ua-tDCS across all comparisons ($d = 0.64 \pm 0.68$; Supplemental Table VI). Moderate to very strong effects were observed on all parameters significantly affected by tDCS (Table 1 and Supplemental Table VI). In direct comparison, kinematic performances were better under bi-tDCS for the largest (or equal) proportions of parameters both across all tasks and for each task (Fig. 5.A).

Permutation tests (Supplemental Material Section 3.3) revealed that the total number of significant comparisons was always larger

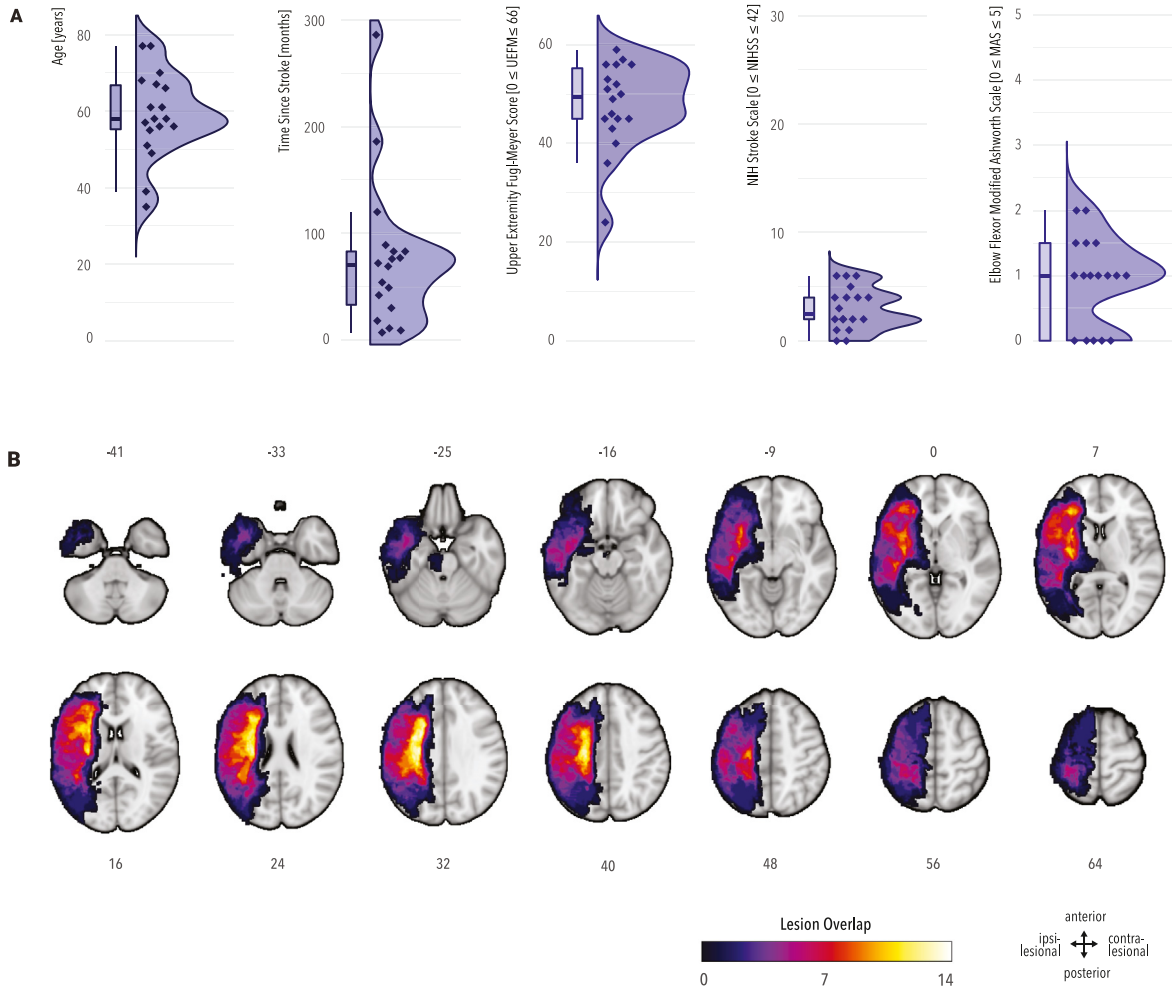


Fig. 3. Patient Sample Description. A Sample information plotted as group-level statistics (box plots) and individual-level distributions (violin plots). **B** Overlap of lesions segmented from DWI and FLAIR images of 20 patients overlaid on the MNI152 T1-template. Labels refer to z-axis. All lesions were flipped to one side to illustrate the heterogeneity of the sample on the brain-level.

than the number of corresponding significant comparisons (both regardless of the direction of the difference) obtained after permuting (corresponding to $p < .001$).

The superiority comparisons indicated no significant difference in ratios between the two setups ($p = .379$).

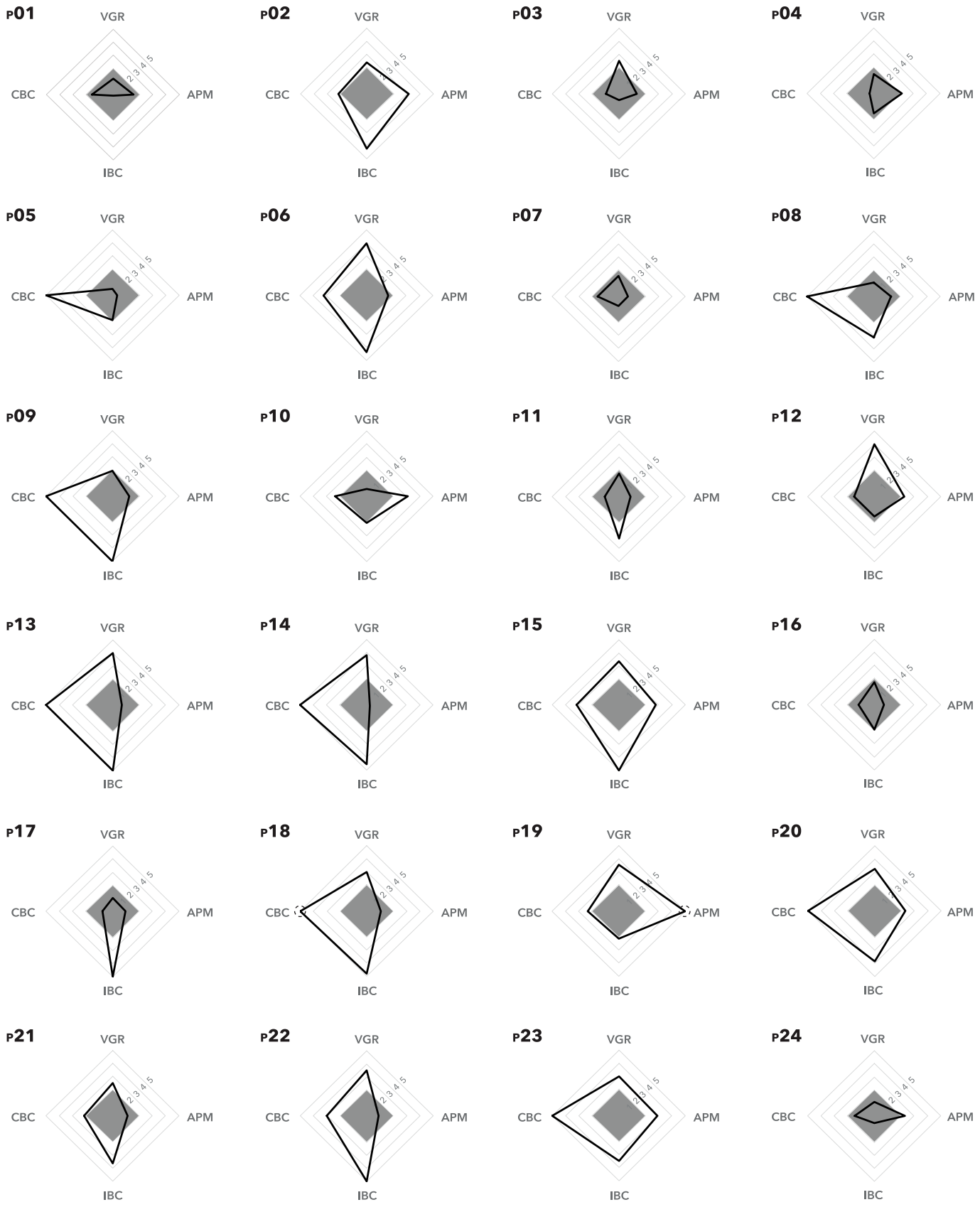
3.2. Inter-parameter correlations

Individual-level modulations largely mirrored group-level results (Fig. 5.A, Supplemental Figures III-VI) as the amount of mutual performance increases, decreases and trade-offs also varied depending on both tasks (Fig. 5.C) and setups (Fig. 5.D). Larger proportions of trade-offs and mutual decreases were identified under ua-tDCS in all tasks, while more mutual increases occurred under bi-tDCS, especially in the VGR and IBC tasks. Altogether, correlation matrices showed that, apart from CBC during ua-tDCS, no task was modulated clearly homogeneously. Rather, especially the presence of trade-off relationships indicates that performance shifts among the parameters of a task can occur in response to tDCS.

4. Discussion

The present study investigated online effects of ua-tDCS and bi-tDCS on paretic arm performance across different sensorimotor tasks testing reaching movements, proprioceptive performance and bilateral coordination in chronic stroke patients. The data demonstrate considerable modulations of sensorimotor functions which, however, did not occur uniformly across either the four robotic tasks or their kinematic parameters: the overall group-level effects were task-dependent with a higher proportion of performance improvements in the unimanual reaching and independent bimanual coordination and deteriorations in the proprioception and cooperative bimanual coordination tasks.

Moreover, effects were different between setups. While there were more parameters affected during bi-tDCS, a direct comparison using Fisher's exact test did not exhibit significant results but conveyed stronger performance increases during bi-tDCS as compared to ua-tDCS. At the individual-level, correlations revealed that tDCS-induced changes in single parameters are complexly related to changes in the other parameters of a respective task and that these change patterns are, task- and setup-specific rather than uniform, contrary to the postulated canonical effects of tDCS. Indeed, our results convey the notion that tDCS in stroke patients induces more complex sensorimotor changes when investigated at a kinematic level: an increase in one parameter might come at the expense of decreases in others (trade-off). Some authors suggested previously that behavioral enhancement induced by non-invasive brain stimulation might the consequence of resource allocation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VGR
APM
IBC
CBC
1 2 3 4 5
Individual Patient Performance (Task Score)
Typical Performance Range (95% Control Sample)
Task Not Performed

Fig. 4. Individual Sensorimotor Deficits. Radar plots represent individual patients with corners corresponding to the overall performance (Task Scores, refer to Supplemental Material Section 3.4. for more detail) in each of the four kinematic tasks of the experiment. Affected arms were tested. Task Scores allow an assessment of individual patient profiles compared to healthy controls, considering performance a-typical if individual scores (black) lie outside of the healthy control norm range (grey). While, most patients exhibited selective impairments in one or more tasks, some (e.g., P01, P07, P16) performed all tasks as well as age-matched controls (despite clinically diagnosed sensorimotor deficits) while others (e.g., P02, P15, P19, P20, P23) showed inferior performance in all tasks. These profiles demonstrate the symptom heterogeneity typically found post-stroke and underscore the need for complex assessment tools. Abbreviations: *APM* = Arm Position Matching (proprioception), *CBC* = Cooperative Bimanual Coordination, *IBC* = Independent Bimanual Coordination, *VGR* = Visually Guided Reaching (unimanual).

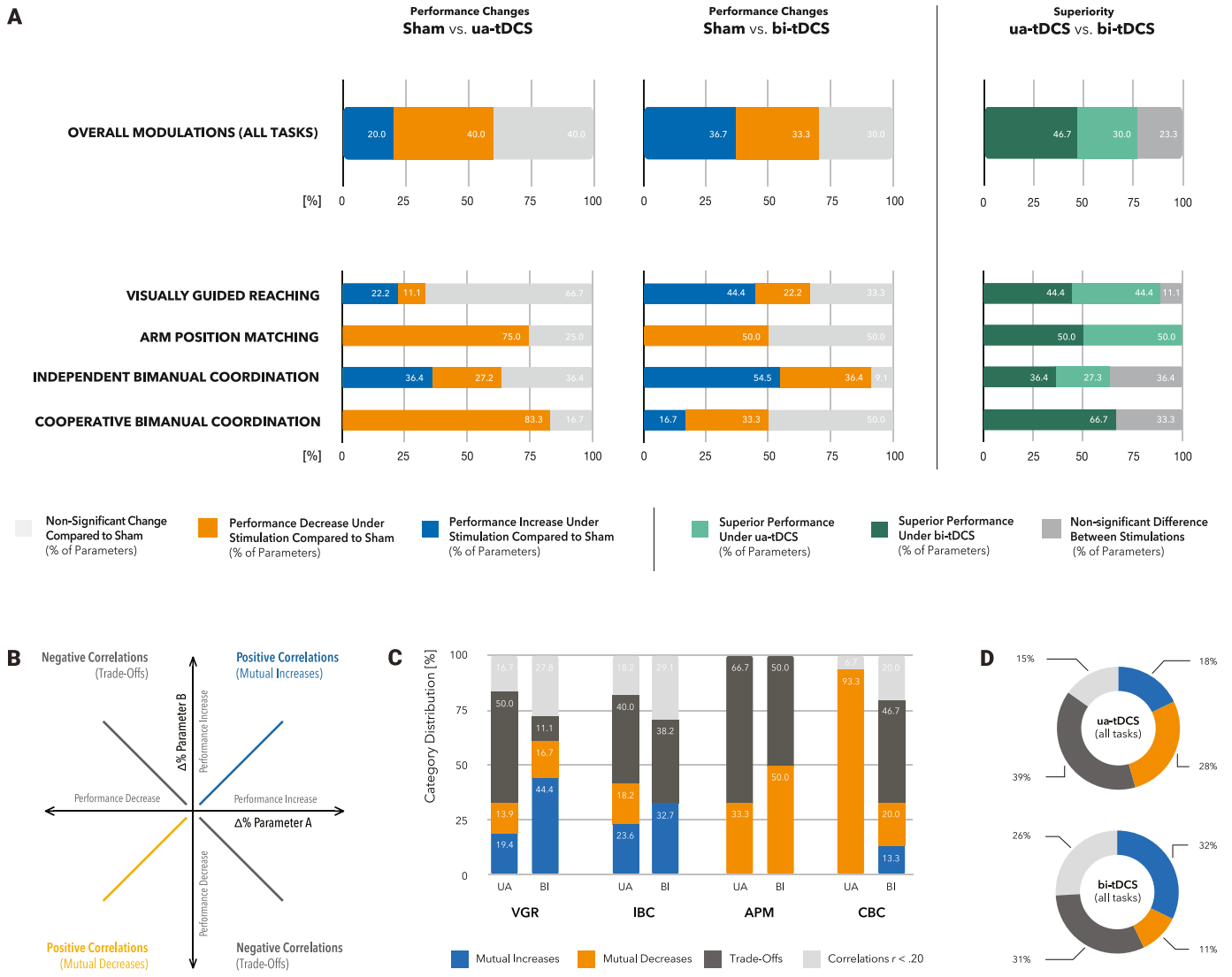

Fig. 5. Overall and Task-wise Performance Changes (Group-Level) and Change Relationships Induced by tDCS (Individual-Level). **A** Count of parameters affected by tDCS provided as percentages [%] of performance change categories for ua-tDCS (left), bi-tDCS (middle) and in direct comparison between ua-tDCS and bi-tDCS (right) across all (upper charts) and separately for each task (lower charts). Statistics for each parameter provided in Table 1. **B** Interpretation key to inter-parametric change score relationships. **C** Task-specific distribution of correlation classes for each setup compared to sham, respectively. **D** Setup-specific distribution of correlation classes across tasks. Color-coding refers to the direction of correlations (panels B & C). For the purpose of a clearer display, correlations coefficients larger than $r > .20$ were considered. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and therefore be accompanied by deterioration in other functions. Indeed, our data convey the notion that this phenomenon - at least partly - might play a role in patients with focal lesions that exhibit even more constrained neural resources. While these results show how intricately specific kinematic aspects of a sensorimotor task are interrelated, they also evince how the selection of outcome parameters can strongly influence the evaluation of tDCS effects. Thus, our findings both confirm and unify the heterogeneous evidence from previous studies and provide a new perspective for the investigation of sensorimotor tDCS effects. On the one hand, our findings are promising for the rehabilitation of sensorimotor deficits after stroke, if they can be translated into training protocols supplemented by tDCS that induce similar and long-lasting effects. On the other hand, the data demonstrate that the optimal tDCS setup will probably have to be chosen individually together with a personalized prioritization of the kinematic aspects to be trained. To make such a personalization reliable and accurate, additional multi-parametric studies will be necessary.

Table 1
Kinematic performance modulations.

PARAMETERS		Sham vs. ua-tDCS					Sham vs. bi-tDCS				
#	Name	Delta [%]		t-Test			Delta [%]		t-Test		
VISUALLY GUIDED REACHING		$\bar{x}_\Delta$	*d*	*t*	*p*	▲	$\bar{x}_\Delta$	*d*	*t*	*p*	▲
1	Posture Speed	**13.15**	**1.4**	**6.911**	**< .001**	↗	4.55	0.2	0.906	0.374	–
2	Reaction Time	**-2.07**	**0.5**	**-2.425**	**0.024**	↘	**-1.41**	**0.5**	**-2.704**	**0.013**	↘
3	Initial Direction Angle	-3.29	0.4	-1.930	0.066	–	**-12.07**	**1.4**	**-6.706**	**< .001**	↘
4	Initial Distance Ratio	-0.75	0.3	-1.774	0.089	–	**-4.10**	**1.2**	**-6.727**	**< .001**	↗
5	Initial Speed Ratio	0.08	0.1	0.374	0.712	–	**-0.34**	**0.4**	**-2.123**	**0.045**	↗
6	Speed Maxima Count	**3.52**	**0.8**	**3.693**	**0.001**	↗	**7.83**	**1.8**	**8.471**	**< .001**	↗
7	Movement Time	0.96	0.2	0.364	0.719	–	**4.67**	**2.0**	**8.12**	**< .001**	↗
8	Path Length Ratio	-0.40	0.3	-1.329	0.197	–	-0.21	0.1	-0.716	0.481	–
9	False Starts	30.86	0.3	1.558	0.133	–	-40.34	0.2	-2.039	0.053	–
ARM POSITION MATCHING											
10	Absolute Error XY	**-20.94**	**1.0**	**-4.717**	**< .001**	↘	**-15.73**	**0.6**	**-2.948**	**0.007**	↘
11	Variability XY	**-13.67**	**2.8**	**-16.934**	**< .001**	↘	**-26.10**	**1.8**	**-8.35**	**< .001**	↘
12	Shift XY	**-32.07**	**0.9**	**-4.505**	**< .001**	↘	-17.85	0.5	-2.037	0.054	–
13	Scaling XY	2.84	0.2	1.873	0.074	–	-0.77	0.1	0.134	0.895	–
INDEPENDENT BIMANUAL COORDINATION											
14	Total Hits	0.04	0.0	-0.102	0.92	–	**-0.50**	**1.0**	**-4.98**	**< .001**	↗
15	Median Error	0.13	0.2	0.999	0.328	–	**0.12**	**0.5**	**2.75**	**0.011**	↘
16	Miss Bias	**-1.02**	**0.0**	**-2.23**	**0.036**	↘	**-46.60**	**0.2**	**-13.85**	**< .001**	↘
17	Hand Bias of Hits	**15.26**	**0.6**	**-3.281**	**0.003**	↗	**-22.02**	**0.7**	**4.75**	**< .001**	↘
18	Hand Transition	35.50	0.2	0.42	0.678	–	**31.78**	**0.1**	**-4.12**	**< .001**	↘
19	Hand Selection Overlap	1.27	0.3	1.408	0.173	–	4.01	0.3	1.37	0.185	–
20	Hand Speed Bias	**23.84**	**2.7**	**-12.802**	**< .001**	↗	**35.71**	**0.7**	**-3.74**	**0.001**	↗
21	Movement Area Bias	**-18.75**	**1.5**	**21.731**	**< .001**	↘	**15.90**	**0.7**	**-3.62**	**0.001**	↗
22	AH Hits	**0.32**	**0.2**	**2.186**	**0.039**	↘	**-2.83**	**1.8**	**-4.44**	**< .001**	↗
23	AH Speed	**-16.25**	**0.5**	**-2.076**	**0.049**	↗	**-18.09**	**0.6**	**-2.13**	**0.044**	↗
24	AH Movement Area	**-17.41**	**0.6**	**-2.128**	**0.044**	↗	**-24.85**	**0.8**	**-3.15**	**0.005**	↗
COOPERATIVE BIMANUAL COORDINATION											
25	Targets Completed	**3.83**	**0.6**	**2.723**	**0.013**	↘	-0.26	0.1	-0.445	0.661	–
26	Mean Movement Time	**-18.72**	**0.7**	**-3.321**	**0.003**	↘	1.44	0.4	1.926	0.068	–
27	AH Speed Maxima Count	**-1.92**	**0.5**	**-2.408**	**0.025**	↘	**-1.40**	**0.6**	**-2.856**	**0.009**	↘
28	Mean Bar Angle	**-55.57**	**0.3**	**-2.457**	**0.023**	↘	-1.21	0.0	0.61	0.548	–
29	Reaction Time Difference	**-15.71**	**0.7**	**-3.315**	**0.003**	↘	**-9.71**	**1.0**	**-4.588**	**< .001**	↘
30	Hand Speed Difference	-1.40	0.21	-1.16	0.258	–	**2.60**	**4.9**	**30.099**	**< .001**	↗

Averaged performance changes on all kinematic parameters (x = mean, d = effect size (Cohen's *d*)). Statistically significant changes are printed in bold and were classified as performance increases (↗) or decreases (↘). Dashes (–) indicate non-significant differences. The distribution of these change categories is illustrated in Fig. 5.A. Individual-level relationships between changes across task parameters are illustrated in Fig. 5.C and 5.D. Extended statistics are provided in Supplemental Table VI. Abbreviations: *AH* = Affected Hand, *XY* = in x- and y-direction.

We deployed the multivariate *t*-test approach for a more detailed description of group-level effect patterns as compared to, for instance, multiple analysis of variance or machine learning classifiers (Supplemental Material Section 3.3). Altogether, both setups induced substantial performance changes on the group-level, confirming our first hypothesis. Concretely, bi-tDCS exhibited both a more pronounced, as more parameters were significantly and more strongly changed irrespective of their directionality, and more beneficial effect than ua-tDCS, as more performance increases and less decreases occurred. These findings confirm our second hypothesis and the general trend in previously published studies [7,41–43], although performance decreases in the magnitude observed in our data have not been previously reported for either setup. The four robotic tasks investigated different sensorimotor functions and were task- and setup-specifically affected: while the highest proportional increases were identified for VGR and IBC, APM and CBC were mainly negatively affected by both setups. Bi-tDCS exhibited a more beneficial effect pattern (i.e., more increases, less decreases) in all individual tasks when compared to ua-tDCS directly.

The simultaneous investigation of multiple parameters per task allowed us to address their interdependence on the individual-level at which task- and setup-specific group-level results were largely mirrored. Notably, significant correlations were identified for numerous parameters that showed no significant modulations on the group-level, underscoring the large inter-individual variability of tDCS effects [44] that can be difficult to capture with conventional mean-based approaches. A more homogeneous modulation across parameters was induced by bi-tDCS, as more positive relationships were identified in all tasks. However, the negative correlations will be of particular interest for future investigations as they can be interpreted to reflect trade-offs between parameters: for instance, a more accurate aiming towards a target (initial direction angle) could come at the “cost” of higher reaction times in the movement planning phase of VGR. If in an individual patient accuracy is considered the primary rehabilitation outcome, such trade-offs in reaction times would therefore unlikely be considered a negative outcome. As a higher proportion of trade-offs occurred for ua-tDCS, the more pronounced group-level performance decreases should therefore only be cautiously interpreted as true performance deteriorations. An alternative interpretation could be that ua-tDCS induces less homogenous effects with more performance shifts between kinematic parameters while bi-tDCS induced rather homogeneous modulations. However, if only trade-offs had occurred across parameters, the overall effects of tDCS would not be considered substantial but rather represent a mere net-zero-sum shift across parameters [45]. However, this can be excluded based on the substantial proportion of positive correlations. Taken together, these results confirm our last hypothesis of complex (i.e., non-uniform) and inter-related effects across task parameters that were specific to the investigated robotic tasks.

As no other multi-parametric study combining tDCS and robotic sensorimotor assessments in stroke patients has been performed, it is difficult to relate our findings to previous work. Only three studies compared the two setups directly in single clinical trials yet: Mahmoudi et al. [43] showed beneficial effects of ua-tDCS and bi-tDCS on the Jebsen-Taylor-Test (without motor training) albeit with stronger changes under bi-tDCS. By contrast, superior effects were demonstrated for ua-tDCS, rather than bi-tDCS, in the studies by Fleming et al. [46], who applied tDCS concurrent to motor learning using the Jebsen-Taylor-Test as outcome, and by O'Shea et al. [47], who compared offline effects of tDCS on reaction times in a pre-post-design. Diverging results might be explained by differences in task design: our experiment was closer to that by Mahmoudi et al., which assessed online tDCS effects rather than motor learning, and our results generally confirm their findings. However, these studies reported behavioral improvements but not declines. Indeed, most studies published so far demonstrated canonical enhancements [8] of task performance while only few studies presented non-canonical responses (null and differential effects [37] or performance decreases [48]), even though disruptive neurophysiological effects following stimulation are conceivable [49]. All previous studies only deployed a limited set of movement parameters, thereby not assessing all aspects of sensorimotor functions. It is feasible that non-canonical effects were not observed as corresponding parameters were simply not measured. When considering the large number of pre-registered trials with hitherto unpublished results [15], the lacking representation of non-canonical effects might well reflect an implicit publication bias in the field [13]. Our findings amalgamate these heterogeneous previous results [12–15] as both canonical and non-canonical modulations occurred depending on the kinematic parameter in question.

In large parts, the hypothesis of bi-tDCS superiority is grounded in the inter-hemispheric imbalance or competition model [50] which assumes that a disbalance of inhibition and excitation between the ipsilesional and contralesional motor cortices post-stroke drives sensorimotor impairments and that tDCS can be used to shift this disbalance to a more healthy ratio. Recent studies, however, questioned the strict application of a perhaps too simplistic interhemispheric imbalance model across patient groups and propose more individualized explanatory models that incorporate additional factors (excitation vs. inhibition, connectivity, time scales of recovery, etc.) [51–53]. For example, it would be feasible to assume that individual interhemispheric imbalance ratios could affect the superiority of a given setup in a way that, for instance, motor outcomes are ameliorated by bi-tDCS in individuals with higher levels, whereas individuals with lower levels show stronger improvements under ua-tDCS. Likewise, patients with stronger deficits could respond differently than mildly affected patients [54].

Many studies have shown beneficial effects of both setups on hand and arm performance post-stroke although an increasing body of literature emerges in which no modulations could be demonstrated, using mostly standardized clinical scales [15]. However, there are no previous studies that investigated the effects of tDCS on sensorimotor performance across different tasks in such detail as presented here. Why did tDCS induce different effects in the tasks tested in our study? The tasks tested in this study comprise various sensorimotor functions and differ in the level of task difficulty. Therefore, they likely engage different neural processes involving distinct brain networks. For example, VGR is a task that tested unilateral visually guided reaching movements of the affected limb. The IBC task is a bilateral task, in which both affected and unaffected arm are required to perform reaching movements, with both limbs operating individually in an alternating fashion. While the CBC task is also a bilateral task, here by contrast to the IBC, both limbs cooperate simultaneously in order to achieve the

goal. Therefore, this task requires simultaneous coordinated bilateral movements and might have a stronger dual-task performance component compared to IBC and therefore a stronger cognitive load. The APM, lastly, is a task that assesses proprioceptive performance of the affected limb. The task design involves a sequence of events with a passive movement of the affected arm followed by a matching movement of the unaffected limb in the absence of visual control. Therefore, also working memory and attention components are required for the performance of this task.

While in VGR and IBC, tDCS rather induced performance increases, in APM and CBC, by contrast, both setups induced mostly performance decreases. In particular, we consider the following reasons for such decreases: Firstly, the tasks differ in their level of sensory information necessary for task performance for cooperative inter-limb coordination [21,23]. In consequence, it is likely that these two tasks, and APM in particular, have higher demands on working memory and attention compared to the two reaching tasks, which poses implications especially for aged individuals [55] like the majority of patients in this sample. Moreover, it is well documented how cortical activity patterns change naturally in the course of aging [56–58] and in response to insults like stroke [59]. These changes are further modulated by the presence and difficulty of motor tasks [60,61] as well as the individual neurophysiology and connectivity post-stroke [52,62]. Indeed, most patients reported these two tasks to be the most difficult for them and two patients could not perform the tasks at all (Fig. 4). As both tDCS setups induced mostly performance decreases here, it appears feasible to assume that brain stimulation interfered with the higher neural demand and evolving network reorganization, potentially as an interaction between disease, age and task difficulty. Secondly, APM and CBC (compared to the other two tasks) differ in their involvement and reliance on the interhemispheric transfer and intermodal integration of information [63]. As mentioned above, VGR and IBC assess ballistic reaching movements during which the two hands operate independently. The underlying neural processing should, accordingly, be mostly intracortical with a stronger reliance on pre-motor to motor and visuomotor integration. For APM, however, visual information is not available and task execution requires the following steps: the passive positioning of the affected arm needs to be sensed. This sensory information is processed in the ipsilesional sensory cortices and needs to be compared to the position of the non-affected arm in the contralesional sensory cortices. To facilitate the active matching, a motor command needs to be formed and executed. Due to the lack of visual input, only proprioceptive information is available and needs to be continuously evaluated until the subjectively correct (mirror-symmetrical) position is assumed. Our results here are supported by our previous demonstration of performance reduction the APM task after ua-tDCS [37] but conflict with findings by Koo that found ua-tDCS beneficial for somatosensory recovery post-stroke [64]. Similarly, in order to move the bar and ball in the CBC task to the target position, both arms need to be in roughly the same (non-mirror-symmetrical) position, which relies on a constant proprioceptive matching between the two arms. Such symmetrical movement patterns likely rely on a much different neuronal coding as unimanual or independent bimanual movements do [65,66]. Taken together, APM and CBC are likely reliant on a neurophysiological basis that is not only largely different from the one that VGR and IBC rely on, but also appears to be affected much dissimilarly by tDCS. As such tasks and their underlying functions are currently underrepresented in the post-stroke tDCS literature, this study provides an important new insight that should be further investigated by future studies.

More generally, performance decreases could have originated from multiple sources. It could be assumed that performance decreases occurred at the cost of performance increases due to limited neural resources [45] or that the cathodal component of ua-tDCS has interfered with online motor learning [67], as the return electrode applied in this study was relatively small. Also, responses could have varied as a function of residual anatomy, physiology and ongoing brain activity [68] but the behavioral data presented here alone cannot address the contribution of these factors. Rather, future studies should complement our findings by also investigating individual physiological changes during tDCS application to elucidate the mechanisms behind our bidirectional effects. Moreover, the incorporation of individual electrical field modeling, measures of transcallosal connectivity or baseline functional activation of the individual sensorimotor system could improve the understanding of such intricate effects as observed here.

We incorporated several *a priori* measures into our experimental design and *post-hoc* quality control steps during analysis (Supplemental Material Section 2) to increase the certainty that any detected effects were attributable to our experimental manipulation rather than methodological artifacts [69]. To increase sampling homogeneity, only patients that met a narrow set of inclusion criteria were enrolled. To acknowledge their typical symptom heterogeneity (Fig. 4) and to reduce the risk for biased outcome parameter selection [70], a multi-parametric assessment was used (Fig. 5). The deployed robotic tasks are reliable measures of sensorimotor functions [20–23], adequate for repeated designs [19] and more sensitive to small performance modulations than clinical scales [18]. We adopted a crossover design to avoid group-wise sampling bias with a relatively large sample size for stroke patients (72 data points).

This study was designed to investigate the instantaneous (online) modulatory potential of tDCS. Previous studies have shown that even a single administration of tDCS over M1 can induce lasting aftereffects of several hours or days [71,72]. When continuously applied to a repeating training, these early effects likely stabilize and increase in strength as a result of motor learning [73], which was, however, not the focus of this experiment. The physiological basis of both processes is described in detail elsewhere [72,74]. Although the above discussion of results by task permits some classification and interpretation of the behavioral modulatory effects of the two tDCS setups on various aspects of sensorimotor function, the data presented here cannot ascertain whether or how such performance changes or patterns of changes across parameters translate to functional changes in activities of daily living – a limitation that many of the previous studies encountered as well. However, certain parameters or parameter types are more frequently and more systematically investigated than others and were shown to have high predictive relationships (ecological validity) with activities of daily living or the extent of stroke recovery. In reaching movements, those include movement time and speed, path length ratios, the number and variability of speed peaks (smoothness), reaction times and (initial) direction errors [75–77]. In proprioceptive tasks, accuracy parameters (endpoint or elbow angle matching errors) showed the strongest relationships with activities of daily living measures [76]. However, as the strength of relationship varies depending on the kinematic parameter and the type of clinical scale or measure of daily activities, temporal parameters, for instance, show generally stronger relationships with temporal components of task completions (e.g., the Action Research Arm Test or the time subscale of the Wolf Motor Function Test) [77]. The question of how certain patterns of changes across these kinematic parameters lead to relevant improvements needs to be addressed in greater detail by future studies.

Our results show that tDCS exerts an immediate performance-modulating effect which would, based on the aforementioned evidence, likely increase when combined with a dedicated sensorimotor training. Moreover, the results highlight the need for a reliable stratification system to prevent non-canonical responses that would inhibit performance progress or even induce performance decreases in extended tDCS-supplemented training regimes. A kinematic-based diagnostic test that is combined with an array of different tDCS setups before a long-term application of tDCS could thus inform a more individualized tDCS approach.

5. Conclusions

Taken together, we identified profound tDCS-induced performance modulations on the group and individual-level that varied depending on the task and applied tDCS setup. The assumed superiority of bi-tDCS over ua-tDCS was replicated, albeit not as clearly as previously postulated. Notably, both setups induced not just performance improvements but also declines in certain parameters which, in some cases, appeared as trade-offs for increasing performance in others. To our knowledge, this is the first demonstration of such effect patterns in the sensorimotor domain. The multi-parametric assessment allows for a more comprehensive evaluation of tDCS that is especially warranted in post-stroke rehabilitation where therapy-induced performance declines are not tolerable. Future studies should further investigate the mechanisms underlying bidirectional changes to better understand the variability of these effects and to enable an individualized tDCS-supplemented neurorehabilitation of sensorimotor deficits. Moreover, additional studies are required that examine in detail how the online effects observed here translate to offline effects and performance changes in longer sensorimotor training protocols.

Credit author statement

Toni Muffel: conceptualization, methodology, formal analysis, investigation, data curation, writing - original draft, writing - review & editing, visualization, project administration.

Pei-Cheng Shih: software, formal analysis, investigation, resources, writing - review and editing, visualization.

Benjamin Kalloch: software, investigation, resources, writing - review & editing, visualization.

Vadim Nikulin: methodology, resources, writing - review & editing, supervision.

Arno Villringer: resources, writing - review & editing, supervision, project administration, funding acquisition.

Bernhard Sehm: conceptualization, methodology, resources, writing - review & editing, supervision, project administration.

Disclosures and conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from muffel@cbs.mpg.de.

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Appendix A. Supplementary Material

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