Bayesian statistics show a lack of change in excitability following bi-hemispheric HD-TDCS over the primary somatosensory cortices

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Disrupting brain activity focally is important to pinpoint which brain regions are involved in a cognitive process. Using small ring electrodes, High Definition transcranial Current Stimulation (HD-tDCS) should increases focality up to 80% compared with standard tDCS [1]. Likewise, simulations using the Finite Element Method (FEM) suggest that using only one cathode and one anode should maximize focality, albeit with reduced current penetration [2].

Here, we share the utility of Bayesian statistics in an attempt to leverage a 1x1 montage using 5.5mm diameter electrodes to focally stimulate the primary somatosensory cortex (SI). The role of SI in cognitive functions has received increasing interest, motivating our desire to interrogate its function [3]. SI is necessary for understanding others people's pain, but whether the hand vs. the face regions of SI support this function remains difficult to investigate without increased focality [4]. Since SI has bilateral receptive fields [5] we were interested in bi-hemispherically stimulating SI. For cognitive neuroscience experiments with moderate sample sizes ($n = 20$), a power analysis shows, a montage would need to have an effect size $d \geq 0.6$ to be useful.

We used an intensity of stimulation similar to previously HD-tDCS studies (1.5 mA), and divided it across hemispheres/anodes (0.75 mA each). We placed one anode on the left between P3 and CP3 and one on the right between P4 and CP4, and the respective cathodes along the central sulcus between CZ and CP1 and between CZ and CP2 (Fig. 1A). Computational models suggest this montage should induce currents over the hand region of SI (Fig. 1A). We used a sham and an active tDCS session per participant, one week apart, in counterbalanced order. In the active stimulation, current was ramped up over 30s, held at 0.75 mA in both anodes for 18 min, and ramped down over 30s. In the sham condition, the current was ramped up and down at the beginning and at the end of the 18 min and kept around 0mA in-between [6]. We measured the effect via Somatosensory Evoked Potentials (SEP; N20, N30, P24 and P45, in particular; Fig. 1B) triggered by stimulation of the right median nerve (square wave pulses, personalized stimulus intensity, frequency of 3 Hz, duration of 500 μs, hands were not visible to the subject; Experiment1: 500 repetitions; Experiment2: 1000 repetitions). For each component, we quantified neuromodulation by comparing the pre-stimulation baseline SEP measurement (t0) with the one taken after real/sham stimulation (t1). We then assessed the tDCS effect using the difference between sham and tDCS, $(t1_{active}\text{-}t0_{active}) - (t1_{sham}\text{ -}t0_{sham})$. To quantify evidence for both the presence and absence of an effect, and estimate the effect size, we used Bayesian t-tests [7]. See Gallo et al., bioRxiv 814780 for more analyses.

Experiment1 ($n = 32$, 17 females, age = 25 ± 5 y, self-reported right handed), moderately suggests that our montage amplifies the SEP component N30 (Fig. 1C), while we have evidence that it did not amplify any of the other components. A traditional frequentist approach would suggest to acquire a second sample to confirm the apparently significant ($p = 0.01$) effect, and a power-analysis suggests $n = 43$ would be necessary. Leveraging sequential Bayesian testing, we decided instead to collected a small number of new, additional participants and monitor whether evidence for the effect remains stable over Experiment2 ($n = 17$, 10 females, age = 22 ± 3 y, self-reported right handed). By itself, Experiment 2 is underpowered ($n = 17$, $d = 0.387$, power = 0.47), and frequentist statistics are uninformative. Bayesian statistics in Experiment 2 alone however showed evidence for the *absence* of the effect observed in Experiment 1 ($BF_{-0} < 1/3$, Fig. 1C). Pooling the data of the two experiments in the sequential analysis, which calculates the evidence for H_1 sequentially with results at $n = x$ considering the data including the first x participants (Fig. 1D), revealed two findings. First, evidence for a lack of effect kept increasing for N20 and stabilized in the moderate zone for P24 and P45. This establishes that our montage does not influence N20, P24 and P45. For N30, instead of providing additional evidence for the desired effect, adding more participants showed that the effect is unstable and fluctuates up and down across participants. Cohen's *d* estimates decreased from the medium effect size of the first 32 participant to a small effect size $d = 0.27$ and no longer included our target $d = 0.6$ in its credibility interval. What we had observed at the end of Experiment 1 (transition between white and grey shading in Fig. 1D) simply was a local maximum in what seems a random fluctuation.

Although our montage thus falls short of providing the desired effect, we submit our experience to share how useful sequential Bayesian testing can be for neurostimulation. In contrast to traditional p values, where $p < 0.05$ arguably provides publishable evidence for an neuromodulation effect, while a non-significant *p*-value does not translate into a likelihood that the null hypothesis

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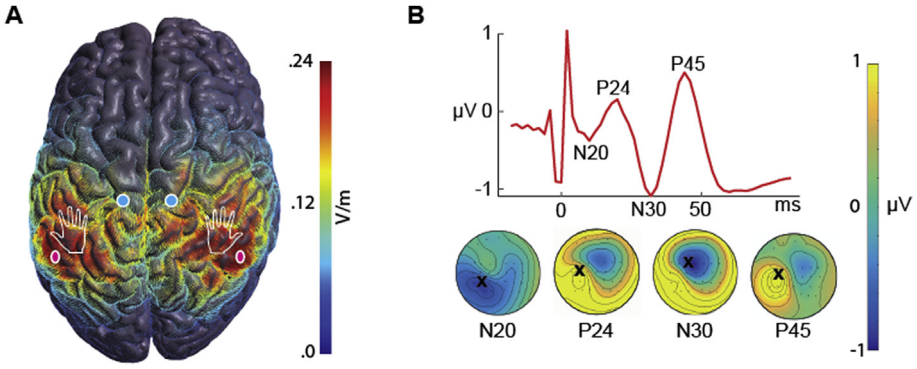

C

		Mean (μV)	SD	t-val.	1 tail Punc	SW Punc	BF_0 or BF_{+0}	BF_{01}	Bayesian Cohen d median & 95% CI
Exp. 1	$N20_{32}$	.09	1.58	.32	.63	.21	.15	5.04	.050 [-.283, .381]
	$P24_{32}$	-.08	1.33	.33	.63	.49	.15	5.03	-.056 [-.384, .282]
	$N30_{32}$	-.46	1.09	-2.39	.01	.18	4.27	.46	-.387 [-.741, -.035]
	$P44_{32}$	.03	1.69	-.19	.46	.51	.21	5.27	.018 [-.313, .355]
Exp. 2	$N20_{17}$	.57	1.10	2.13	.97	.49	.09	.67	.438 [-.020, .947]
	$P24_{17}$	.06	1.04	.25	.40	.83	.30	3.90	.051 [-.388, .492]
	$N30_{16}$	.17	.44	1.57	.69	.22	.11	1.42	.065 [-.372, .505]
	$N30_{17}$	.05	.65	.34	.63 (.84)	.01	.20 (0.32)	3.82 (3.14)	.070 [-.366, .521]
	$P44_{17}$	-.36	.88	-1.70	.95	.32	.11	1.22	-.347 [-.835, .108]
Exp. 1 & Exp. 2	$N20_{49}$	.26	1.44	1.24	.89	.08	.07	3.13	.166 [-.103, .440]
	$P24_{49}$	.03	1.23	-.16	.56	.29	.14	6.36	-.021 [-.294, .251]
	$N30_{49}$	-.28	.99	-2.00	.01 (.14)	.03	1.89 (.90)	1.03 (2.13)	-.268 [-.549, .016]
	$P44_{49}$	-.10	1.46	-.50	.69	.21	.11	5.72	-.067 [-.341, .199]

D

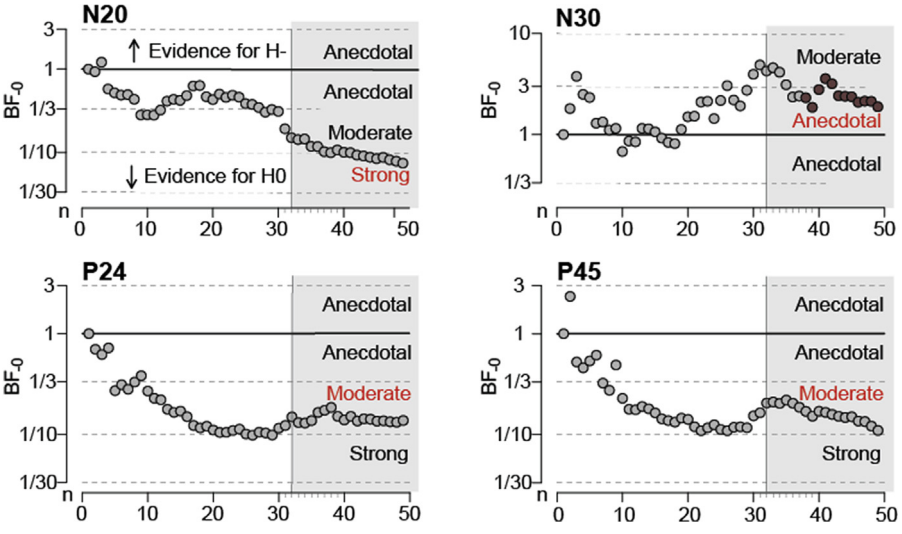

Fig. 1. A) Numerical simulation of the electric field generated by our HD-tDCS montage with reference to anodes (red dots), cathodes (blue dots) and the hand representations (white outlines) in both left and right SI. The simulation was run using simNIBS 3.1.0 and was based on a high-quality FEM model (Ernie.msh). The coloured lines represent the strength and direction of the electric field caused by our stimulation in the brain tissue. **B)** SEP obtained by averaging the signal recorded in C3 at T0 (i.e. before HD-tDCS stimulation) across experiments, with below, the scalp topography of the SEP components obtained by averaging the T0-grand average of experiment 1 and 2 in the appropriate time-windows. Bold Xs indicate the location of the electrodes chosen as peak of the component. **C)** For each ERP component the table reports: the mean value in μV of the HD-tDCS effect index [(t1active-t0 active) - (t1sham -t0 sham)]; its standard deviation (SD); the t- and uncorrected p-value from the frequentist statistic, and in brackets the p resulting from the non-parametric Wilcoxon *t*-test when normality was violated (H_-: index<0 for N20 and N30, and H_+ index>0 for P24 and P45); the Shapiro-Wilk (SW) normality test; the results of the one-tailed Bayesian analysis in favour of H_+ or H_- (BF_{-0} or BF_{+0} as appropriate) and two-tailed Bayesian analysis in favour of H_0 (BF_{01}), with in brackets the non-parametric Bayesian values, computed as in (van Doorn et al., arXiv:1712.06941.t); the Bayesian Cohen's d with the 95% credibility interval (CI) from the two-tailed Bayesian testing. A meta-analysis suggests that for tDCS over sensorimotor cortices the anode causes an enhancement of cortical excitability and thus we expect an enhancement of the SEP components from our montage. The Bayesian analyses has been run using the default Cauchy prior ($r = 0.707$). Sample sizes indicated as subscript of each component, df are therefore n-1. In red are the significant results, using $p = 0.05$ and $BF = 3$ as the critical values. For the component N30 one subject in Exp. 2 was removed as it would drive the distribution away from normality ($N30_{17}$, $p < 0.01$). When combining the data of the two experiments, normality was again violated for N30. **D)** Cumulative probabilities of the data given our hypotheses for each added participant. The grey area indicates the pool of participant coming from Experiment 2. The beginning of darker dots in the N30 plot indicates that from that point onward ($n = 38$) the N30 distribution violates normality (Shapiro-Wilk W=.94 with p=.042). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

is true [8], the Bayes factor allows us to quantify the relative evidence for and against the null hypothesis, and to monitor it continually as data accumulate [9,10]. Here, this affords two valuable opportunities. First, it allowed us, already with our initial sample to provide evidence that our HD-tDCS montage, despite delivering some current to SI (Fig. 1A), does not alter N20, P24 or P45. Second, using sequential testing, we could include data from a growing number of additional participants, and monitor the impact this had on our initial findings without needing a large predefined replication group. This confirmed our evidence of absence of an effect on N20, P24 or P45. Most importantly, for N30, where the credibility interval on the effect size was initially encouraging although too broad to be conclusive, this sequential testing allowed us to discontinue testing once it became apparent that effect size estimates became too small for our intended use. With a revised estimate of only $d = 0.268$, a power analysis reveals that 87 participants would be required to achieve 80% power at alpha $= 0.05$ in any cognitive study with such a montage.

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