Aus dem Institut der Klinik für Neurologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Lang anhaltende Verbesserung der visuellen Wahrnehmung durch wiederholte, nicht invasive transkranielle Gleichstromstimulation

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von

Janina R. Behrens

aus Lübeck

Datum der Promotion: .....7.12.18.....

What counts is not what sounds plausible, not what we would like to believe, not what one or two witnesses claim, but only what is supported by hard evidence rigorously and skeptically examined.

— Carl Sagan

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1.1 Abstract auf Deutsch

Lang anhaltende Verbesserung der visuellen Wahrnehmung durch wiederholte, nicht invasive transkranielle Gleichstromstimulation

Hintergrund/Ziel: Die neuronalen Prozesse des intakten visuellen Kortex als Basis für die Entwicklung von Methoden zu untersuchen, die die visuelle Wahrnehmung verbessern oder wiederherstellen, ist sowohl für Forscher als auch für praktizierende Ärzte von großem Interesse. In dieser Studie untersuchen wir, ob die Kontrastempfindlichkeit, als eine Hauptfunktion des primären visuellen Kortex (V1), bei gesunden Probanden durch wiederholte, nicht invasive anodale transkranielle Gleichstromstimulation (tDCS) verbessert werden kann.

Methoden: Die Kontrastwahrnehmung wurde mit einer Schwellenperimetrie direkt vor und nach der Intervention (tDCS- oder Pseudo-Stimulation) an jedem Tag und über 5 aufeinanderfolgende Tage bestimmt (24 Probanden, Doppelblindstudie).

Ergebnisse: tDCS verbesserte signifikant die Kontrastwahrnehmung ab dem zweiten Tag und die Effekte hielten über 24 Stunden an. Nach der letzten Stimulation am fünften Tag zeigte die tDCS-Gruppe eine signifikant größere Verbesserung der Kontrastwahrnehmung im Vergleich zur Placebo-Gruppe (23% gegenüber 5%). Wir fanden vier Wochen nach der letzen Stimulation nur in den zentralen 2-4° des Gesichtsfeldes signifikante Langzeit-Effekte.

Schlussfolgerung:
Wir vermuten, dass eine Kombination von zwei Faktoren zu diesen Langzeit-Effekten beiträgt: Erstens befindet sich der V1-Bereich, der die zentrale Netzhaut repräsentiert, näher bei der Polarisationselektrode, was zu einer höheren Stromdichte führt. Zweitens wird das zentrale Gesichtsfeld durch einen größeren kortikalen Bereich gegenüber dem peripheren Gesichtsfeld (*cortical magnification;* kortikale Vergrößerung) dargestellt.

Die ist die erste Studie, die zeigen konnte, dass tDCS über V1 die Kontrastwahrnehmung bei gesunden Probanden für mehrere Wochen verbessert. Die Studie trägt damit zur Untersuchung des kausalen Zusammenhangs zwischen der externen Modulation des neuronalen Membranpotentials und des Verhaltens (in unserem Fall der visuellen Wahrnehmung) bei. Weil die überwiegende Mehrheit der Studien beim Menschen nach einer einzelnen tDCS-Applikation nur temporäre Effekte auf das visuelle System zeigen konnte, zeigt unsere Studie – bei wiederholter tDCS-Applikation – das Potenzial für dauerhafte Effekte auf, in Form einer langanhaltenden Modulation der neuronalen Erregbarkeit.

1.2 Abstract auf Englisch

Long-lasting enhancement enhancement of visual perception with repetitive noninvasive transcranial direct current stimulation

Background: Understanding processes performed by an intact visual cortex as the basis for developing methods that enhance or restore visual perception is of great interest to both researchers and medical practitioners. Here, we explore whether contrast sensitivity, a main function of the primary visual cortex (V1), can be improved in healthy subjects by repetitive, noninvasive anodal transcranial direct current stimulation (tDCS).

Methods: Contrast perception was measured via threshold perimetry directly before and after intervention (tDCS or sham stimulation) on each day over 5 consecutive days (24 subjects, double-blind study).

Results: tDCS improved contrast sensitivity from the second day onwards, with significant effects lasting 24 hours. After the last stimulation on day 5, the anodal group showed a significantly greater improvement in contrast perception than baseline and the sham group (23% vs. 5%). We found significant long-term effects in only the central 2–4° of the visual field 4 weeks after the last stimulation.

Conclusion: We suspect a combination of two factors contributes to these lasting effects. First, the V1 area that represents the central retina was located closer to the polarization electrode, resulting in higher current density. Second, the central visual field is represented by a larger cortical area relative to the peripheral visual field (cortical magnification).

This is the first study showing that tDCS over V1 enhances contrast perception in healthy subjects for several weeks. This study contributes to the investigation of the causal relationship between the external modulation of neuronal membrane potential and behavior (in our case, visual perception). Because the vast majority of human studies only show temporary effects after single tDCS sessions targeting the visual system, our study underpins the potential for lasting effects of repetitive tDCS-induced modulation of neuronal excitability.

2.1 Eidesstattliche Versicherung

„Ich, Janina R. Behrens, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema „Lang anhaltende Verbesserung der visuellen Wahrnehmung durch wiederholte, nicht invasive transkranielle Gleichstromstimulation“, selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -www.icmje.org) kenntlich gemacht.
Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o.) und werden von mir verantwortet.
Mein Anteil an der ausgewählten Publikation entspricht dem, der in der unten stehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben ist.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

2.2.1 Ausführliche Anteilserklärung an der erfolgten Publikation

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Publikation als federführende Erstautorin in einem Top Journal, das unter den ersten 30 % der nach Impact Factor sortierten Journale des Fachgebietes und mit einem Eigenfaktor über 0,01 liegt.

Autoren:
Janina R. Behrens, Antje Kraft, Kerstin Irlbacher, Holger Gerhardt, Manuel C. Olma, Stephan A. Brandt

Titel:
Long-lasting enhancement of visual perception with repetitive noninvasive transcranial direct current stimulation

Journal:
Frontiers in Cellular Neuroscience

Datum der Online-Veröffentlichung:
15.08.2017

2.2.2 Beitrag im Einzelnen:

Die Studie und die vorliegende Publikation wurden in gemeinschaftlicher Zusammenarbeit mit den Co-Autoren Dr. Manuel C. Olma, Dr. Antje Kraft und Dr. Kerstin Irlbacher an der Klinik für Neurologie an der Charité – Universitätsmedizin Berlin in der Arbeitsgemeinschaft *Vision & Motor System Group - Stephan Brandt* unter der Leitung von Prof. Dr. med. Stephan A. Brandt durchgeführt.

Planung des Studiendesigns: Der Planung des Studiendesigns ging eine etwa sechsmonatige Phase der ausführlichen Literaturrecherche voraus, die von mir selbsttätig durchgeführt wurde. Im monatlichen Abstand wurden in dieser Zeit Abschnitte der Literaturrecherche ausführlich mit meinem Co-Autor Dr. Olma sowie mit Prof. Brandt kritisch diskutiert. Die abschließende Planung des Studiendesigns führte ich in Zusammenarbeit mit Prof. Brandt, Dr. Olma, Dr. Kraft und Dr. Irlbacher durch.

Probanden-Rekrutierung: Die Probanden-Rekrutierung wurde von mir durch Ausschreibungen in den Semester-Verteilern der Charité sowie mithilfe von Aushängen an der Humboldt- und Freien Universität zu Berlin durchgeführt. Ebenso führte ich die Terminplanung sowie die Probandenbetreuung komplett eigenverantwortlich und selbstständig durch.

Durchführung der Studie: Ich wurde von Dr. Olma sowie teilweise auch von Dr. Robert Fleischmann aus der AG *Vision & Motor System Group* in den unten aufgeführten Methoden der Studie vor Studienbeginn angelernt. Dr. Olma supervidierte dabei die Durchführung einer Pilotmessung meinerseits und stand im Verlauf der Studie bei technischen Fragen zur Verfügung. Die Studiendurchführung mit den im Folgenden aufgelisteten Messmethoden wurden von mir komplett selbstständig und eigenverantwortlich durchgeführt.

MRT-Messungen: Nach einer entsprechenden Sicherheitsbelehrung am Campus des Virchow-Klinikums der Charité, führte ich am dortigen Campus bei allen Probanden eigenständig eine MRT-Messung durch (1.5 Tesla Magnetom VisionMRI scanner, Siemens, Erlangen). Die Messungen bestanden aus einer T1-gewichteten Sequenz (magnetization-prepared rapid gradient-echo, MP-RAGE) und dienten zur Elektrodenpositionierung für die tDCS-Applikationen (siehe auch folgende Punkte).

Navigation der Elektrodenposition, Durchführung der tDCS- und Perimetrie-Messungen: Die MRT-Aufnahmen wurden genutzt, um bei individueller Variabilität der Lage des primären visuellen Kortex (V1), die korrekte Elektroden-Position bestimmen zu können. Hierfür wurden mithilfe einer speziellen Infrarotkamera (Polaris Spectra, Northern Digital Inc., ON, Canada) und reflektierendem Marker, anatomische Landmarken des Schädels aufgesucht. Ein Abgleich zwischen der Kopfoberfläche der Probanden und ihrer anatomischen MRT-Daten (MP-RAGE) wurde dann durch ein spezielles Navigationssystems berechnet (Nexstim Eximia Navigated Brain Stimulation System, Helsinki, Finland). Die Bestimmung der Elektrodenposition wurde zu Studienbeginn des jeweiligen Probanden einmalig durchgeführt. Die Zuteilung der Codes für Pseudo- und Real-tDCS-Applikation wurde durch Dr. Olma vorgenommen, sodass ich verblindet die tDCS-Anwendungen durchführen konnte. Vor Studienbeginn lernte ich die Probanden in jeweils drei Durchgängen an, die Perimetrie korrekt zu bedienen. Die Perimetrie-Messung erfolgte dann jeweils vor und nach der tDCS- beziehungsweise Pseudo-Stimulation. Jeder der 24 Probanden erhielt an fünf aufeinander folgenden Tagen die tDCS- bzw. Pseudo-tDCS-Anwendung. An zwei Follow-Up-Terminen wurde nach jeweils zwei als auch vier Wochen eine Perimetrie-Messung zur Prüfung möglicher Langzeiteffekte durchgeführt. Alle genannten Messungen wurden durch mich selbstständig und eigenverantwortlich durchgeführt, beziehungsweise bei teils eigenständiger, durch den Probanden durchgeführter Perimetrie-Messung (Druck eines Knopfes bei Lichtpunktwahrnehmung), von mir betreut.

Datenverwaltung: Die kompletten Datenpunkte des Gesichtsfeldes jedes Probanden und jeder Perimetrie-Messung wurden in eine hierfür von mir programmierte SQL-Datenbank eingegeben. Zur Sicherung der Datenqualität wurden durch Zufallsprinzip durch Dr. Olma zugeloste Stichproben mit den Quelldaten abgeglichen (insgesamt ca. 10% der Gesamt-Daten).

Statistische Auswertung, Datenanalyse und Datenaufbereitung: Die komplette statistische Auswertung und Datenanalyse wurde von mir selbsttätig und eigenverantwortlich mit der Statistik-Software SPSS durchgeführt (Version 19, IBM, Somers, NY, USA). Die Rechen- und Analysewege wurden von Dr. Olma supervidiert und die Ergebnisse wurden mit Prof. Brandt und Dr. Olma zusammen interpretiert und bewertet. Die Aufbereitung der Daten und Anfertigung aller statistischen Abbildungen wurde eigenverantwortlich von mir durchgeführt. Eine Illustration der Stimulationsbedingungen und des Studiendesigns der ersten Publikations-Abbildung (siehe Figure 1 der Publikation) wurde dabei durch *Elsevier Illustration Services* auf Basis der originalen Bilddaten durchgeführt (Bildrechte liegen bei meiner Person).

Verfassen sowie Bearbeiten der Publikation: Die Konzeption der Publikation und die inhaltliche Struktur wurden anhand der Ergebnisse von mir und unter Supervision von Prof. Brandt vorgenommen. Alle Abschnitte der ersten Fassung des Manuskriptes wurden von mir verfasst und nach inhaltlicher und konzeptueller Bearbeitung sowie unter kritischer Durchsicht und Korrektur der Co-Autoren Prof. Brandt, Dr. Olma und Dr. Kraft von mir überarbeitet. Somit wurde die Publikation bis zur Einreichung beim Journal maßgeblich federführend durch mich fertiggestellt. Die entsprechenden Abbildungen fertigte ich für die Publikation in selbständiger Arbeit an, wobei eine Abbildung (im obigen Punkt erwähnt) durch *Elsevier Illustration Services* endbearbeitet wurde. Abschließend wurde die aktuelle Fassung der Publikation auch unter Berücksichtigung der Korrekturvorschläge der unabhängigen Reviewer/Gutachter des Journals *Frontiers in Cellular Neuroscience* von Dr. Olma, Dr. Gerhardt und mir überarbeitet.

Beitrag bei einer weiterführenden Studie und Publikation: Als Co-Autorin wirkte ich bei einer parallel begonnenen Studie bei Schlaganfall-Patienten mit, die ein weitgehend analoges Studiendesign zur vorliegenden Arbeit aufwies. Die Veröffentlichung erfolgte ebenfalls in einem *Top Journal,* das unter den ersten 30 % der nach Impact Factor sortierten Journale des Fachgebietes und mit einem Eigenfaktor über 0,01 liegt (s. auch Literaturliste):

Olma MC, Dargie RA, Behrens JR, Kraft A, Irlbacher K, Fahle M, Brandt SA, Long-Term Effects of Serial Anodal tDCS on Motion Perception in Subjects with Occipital Stroke Measured in the Unaffected Visual Hemifield, Frontiers in Human Neuroscience, 2013.

Beitrag im Einzelnen: Die Planung des Studiendesigns wurde anteilig von mir in Zusammenarbeit mit Prof. Brandt und Dr. Olma durchgeführt. Eine ausführliche Literaturrecherche wurde ebenfalls anteilig von mir in Zusammenarbeit mit Dr. Olma sowie dem Studenten Richard A. Dargie durchgeführt, der mit der Durchführung der Studie im Rahmen seiner Master-Arbeit betraut werden sollte. Zusammen mit Herrn Dargie führte ich die Patienten-Rekrutierung unter Supervision des Centrums für Schlaganfallforschung Berlin (CSB) durch und erstellte mit Herrn Dargie die Terminplanung. Herr Dargie lernte unter Dr. Olmas und meiner Supervision die Messmethoden der Studie, damit die eigenständige Durchführung der MRT-Messungen, Navigation der Elektrodenposition, tDCS-Anwendung sowie Durchführung der Perimetrie- und Campimetrie-Messungen. Während der Studie führte ich hinzu anteilig und eigenverantwortlich die MRT-Messungen sowie Eletrodenpositionierung bei einem Teil der Studien-Patienten mit analogen Gerätschaften und MR-Sequenzen der bereits genannten Messmethoden der Probandenstudie durch. Die statistische Auswertung der Messergebnisse wurde wiederum von mir anteilig und in Zusammenarbeit mit Dr. Olma und Herrn Dargie durchgeführt. Die Publikation wurde maßgeblich federführend von Dr. Oma in Zusammenarbeit mit Herrn Dargie fertiggestellt. Die kritische Durchsicht der Publikation erfolgte unter anderem durch mich als Co-Autorin.

2.3 Unterschrift Hochschullehrer und Doktorandin

3. Auszug aus der Journal Summary List® (entspr. ISI Web of Knowledge℠):

Nach den Journal Citation Reports (JCR) 2016 ist das Journal *Frontiers in Cellular Neuroscience* im Fachbereich *Neuroscience* von insgesamt 258 nach Impact Factor sortierten Journalen auf Rang 55 (s. Anhang S. II) gelistet und liegt damit innerhalb der oberen 30 %. *Frontiers in Cellular Neuroscience* hat einen Impact Factor von 4,555 und einen Eigenfaktor von 0,0275 und gehört damit zu den *Top Journals*.

Anhang A Seiten I–VI

Journal Data Filtered By: Selected JCR Year: 2016 Selected Editions: SCIE Selected Categories: 'NEUROSCIENCES' Selected Category Scheme: WoS

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE REVIEWS NEUROSCIENCE	36,952	28.880	0.071380
2	NATURE NEUROSCIENCE	54,399	17.839	0.160740
3	Annual Review of Neuroscience	13,211	15.630	0.020660
4	TRENDS IN COGNITIVE SCIENCES	23,273	15.402	0.046360
5	BEHAVIORAL AND BRAIN SCIENCES	8,195	14.200	0.010940
6	NEURON	82,253	14.024	0.227070
7	PROGRESS IN NEUROBIOLOGY	12,163	13.217	0.018020
8	MOLECULAR PSYCHIATRY	17,452	13.204	0.049670
9	ACTA NEUROPATHOLOGICA	16,462	12.213	0.037060
10	BIOLOGICAL PSYCHIATRY	41,859	11.412	0.067400
11	TRENDS IN NEUROSCIENCES	19,178	11.124	0.029690
12	JOURNAL OF PINEAL RESEARCH	7,278	10.391	0.008040
13	BRAIN	48,061	10.292	0.077590
14	ANNALS OF NEUROLOGY	34,215	9.890	0.057310
15	FRONTIERS IN NEUROENDOCRINOLOGY	3,516	9.425	0.006600
16	SLEEP MEDICINE REVIEWS	4,980	8.958	0.009730
17	NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS	20,452	8.299	0.047230
18	NEUROSCIENTIST	4,325	7.391	0.009890
19	Molecular Neurodegeneration	2,946	6.780	0.009540
20	CEREBRAL CORTEX	27,496	6.559	0.063240
21	NEUROPSYCHOPHARMACOLOGY	23,920	6.403	0.046670
22	NEUROPSYCHOLOGY REVIEW	2,478	6.352	0.004650
23	GLIA	12,781	6.200	0.021920
24	Alzheimers Research & Therapy	1,699	6.196	0.007180
25	MOLECULAR NEUROBIOLOGY	7,338	6.190	0.017440
26	NEUROSIGNALS	653	6.143	0.000670
27	CURRENT OPINION IN NEUROBIOLOGY	13,188	6.133	0.036730
28	Brain Stimulation	3,905	6.078	0.013020
29	JOURNAL OF NEUROSCIENCE	171,800	5.988	0.319910
30	BRAIN BEHAVIOR AND IMMUNITY	10,719	5.964	0.026460
31	NEUROIMAGE	85,630	5.835	0.173210
32	PAIN	35,333	5.445	0.044460
33	NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY	3,413	5.347	0.006400
34	NEURAL NETWORKS	8,741	5.287	0.010250
35	BRAIN PATHOLOGY	4,580	5.272	0.008450
36	JOURNAL OF NEUROTRAUMA	12,787	5.190	0.021640
37	Neurotherapeutics	3,451	5.166	0.008220
38	JOURNAL OF PSYCHIATRY & NEUROSCIENCE	2,759	5.165	0.004970
39	NEUROBIOLOGY OF AGING	20,010	5.117	0.046250
40	Journal of Neuroinflammation	7,946	5.102	0.023970
41	JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM	16,998	5.081	0.029520
42	Frontiers in Molecular Neuroscience	1,979	5.076	0.008520

43	NEUROBIOLOGY OF DISEASE	14,554	5.020	0.031140
44	NEUROPHARMACOLOGY	18,559	5.012	0.040280
45	SLEEP	18,127	4.923	0.026090
46	Multiple Sclerosis Journal	9,727	4.840	0.023240
47	Molecular Autism	1,294	4.833	0.006320
48	PSYCHONEUROENDOCRINOLOGY	14,409	4.788	0.028830
49	Neuropsychiatry	149	4.778	0.000740
50	JOURNAL OF PHYSIOLOGY-LONDON	48,567	4.739	0.047830
51	INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY	6,082	4.712	0.015310
52	EXPERIMENTAL NEUROLOGY	19,445	4.706	0.027440
53	CURRENT OPINION IN NEUROLOGY	5,258	4.699	0.011490
54	Brain Structure & Function	4,325	4.698	0.014300
55	Frontiers in Cellular Neuroscience	6,088	4.555	0.027500
56	BIPOLAR DISORDERS	5,323	4.531	0.009660
57	HUMAN BRAIN MAPPING	18,139	4.530	0.041900
58	JOURNAL OF PAIN	8,312	4.519	0.018540
59	Frontiers in Aging Neuroscience	3,477	4.504	0.013020
60	Developmental Cognitive Neuroscience	1,483	4.321	0.007490
61	CORTEX	8,200	4.279	0.021370
62	EUROPEAN NEUROPSYCHOPHARMACOLOGY	6,575	4.239	0.015920
63	PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY	9,740	4.187	0.016310
64	JOURNAL OF PSYCHOPHARMACOLOGY	5,518	4.179	0.012020
65	JOURNAL OF NEUROCHEMISTRY	35,279	4.083	0.030170
66	EUROPEAN JOURNAL OF NEUROLOGY	9,137	3.988	0.018850
67	Dialogues in Clinical Neuroscience	2,348	3.976	0.005480
68	HIPPOCAMPUS	8,694	3.945	0.016170
69	Social Cognitive and Affective Neuroscience	5,263	3.937	0.020160
70	CNS Neuroscience & Therapeutics	2,615	3.919	0.007370
71	Annals of Clinical and Translational Neurology	902	3.901	0.004880
72	ACS Chemical Neuroscience	3,084	3.883	0.011020
73	Frontiers in Neuroinformatics	1,377	3.870	0.006310
74	CLINICAL NEUROPHYSIOLOGY	17,871	3.866	0.021920
75	NUTRITIONAL NEUROSCIENCE	1,192	3.765	0.001900
76	GENES BRAIN AND BEHAVIOR	3,385	3.743	0.006820
77	JOURNAL OF ALZHEIMERS DISEASE	14,542	3.731	0.036370
78	NEUROGASTROENTEROLOGY AND MOTILITY	6,608	3.617	0.016200
79	CEPHALALGIA	7,932	3.609	0.011650
80	NEUROENDOCRINOLOGY	4,525	3.608	0.005060
81	Journal of Neurodevelopmental Disorders	825	3.582	0.003040
82	JOURNAL OF HEADACHE AND PAIN	2,141	3.580	0.004980
83	Frontiers in Neuroscience	6,489	3.566	0.027070
84	Frontiers in Neurology	3,192	3.552	0.014480
85	NEUROBIOLOGY OF LEARNING AND MEMORY	5,862	3.543	0.012320
86	Molecular Pain	2,975	3.533	0.007370
87	Journal of NeuroEngineering and Rehabilitation	3,323	3.516	0.007320
88	JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY	8,483	3.503	0.009270
89	JOURNAL OF NEUROENDOCRINOLOGY	5,524	3.470	0.007680
90	Journal of Neural Engineering	4,693	3.465	0.011570
91	Cognitive Computation	795	3.441	0.001670

92	Molecular Brain	1,778	3.410	0.006030
93	BRAIN TOPOGRAPHY	2,155	3.394	0.004500
94	Current Neuropharmacology	2,087	3.365	0.003690
95	Current Neurology and Neuroscience Reports	2,294	3.345	0.006630
96	Journal of Neuroimmune Pharmacology	2,199	3.339	0.005540
97	PSYCHOPHARMACOLOGY	23,655	3.308	0.030960
98	NEUROMOLECULAR MEDICINE	1,641	3.287	0.002890
99	NEUROPSYCHOLOGY	5,422	3.286	0.007930
100	NEUROSCIENCE	44,046	3.277	0.060260
101	Frontiers in Neuroanatomy	1,975	3.267	0.009260
102	JOURNAL OF COMPARATIVE NEUROLOGY	29,871	3.266	0.018330
103	COGNITIVE AFFECTIVE & BEHAVIORAL NEUROSCIENCE	3,303	3.263	0.007260
104	NEUROCHEMISTRY INTERNATIONAL	7,819	3.262	0.011400
105	JOURNAL OF SLEEP RESEARCH	4,390	3.259	0.006910
106	CEREBELLUM	2,155	3.234	0.005740
107	Frontiers in Human Neuroscience	12,836	3.209	0.056590
108	JOURNAL OF NEUROVIROLOGY	2,487	3.206	0.004340
109	NEUROINFORMATICS	1,043	3.200	0.003960
110	NEUROPSYCHOLOGIA	23,509	3.197	0.034950
111	JOURNAL OF COGNITIVE NEUROSCIENCE	16,713	3.108	0.027250
112	Frontiers in Behavioral Neuroscience	4,319	3.104	0.018660
113	NEUROTOXICOLOGY	6,005	3.100	0.007880
114	MOLECULAR AND CELLULAR NEUROSCIENCE	6,529	3.084	0.009130
115	NEURAL PLASTICITY	2,131	3.054	0.006420
116	BRAIN RESEARCH BULLETIN	8,761	3.033	0.007430
116	DEVELOPMENTAL NEUROSCIENCE	2,028	3.033	0.002940
118	ASN Neuro	781	3.030	0.002470
119	Purinergic Signalling	1,494	3.022	0.003400
120	EUROPEAN JOURNAL OF PAIN	6,221	3.019	0.011280
121	Frontiers in Neural Circuits	2,117	3.005	0.012100
122	BEHAVIOURAL BRAIN RESEARCH	23,285	3.002	0.040590
123	Developmental Neurobiology	2,624	2.972	0.008870
124	NEUROMUSCULAR DISORDERS	4,283	2.969	0.008960
125	Current Alzheimer Research	3,244	2.952	0.007700
126	NEUROTOXICITY RESEARCH	2,357	2.942	0.003690
127	EUROPEAN JOURNAL OF NEUROSCIENCE	26,124	2.941	0.032090
128	CELLULAR AND MOLECULAR NEUROBIOLOGY	3,642	2.939	0.005390
129	HEARING RESEARCH	8,833	2.906	0.011270
130	LEARNING & MEMORY	5,835	2.894	0.008950
131	Neurodegenerative Diseases	1,509	2.842	0.003880
132	PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR	12,453	2.748	0.011780
133	BRAIN RESEARCH	54,957	2.746	0.041790
134	Neurophotonics	243	2.740	0.001220
135	JOURNAL OF NEUROIMMUNOLOGY	9,420	2.720	0.010610
136	JOURNAL OF PHYSIOLOGY-PARIS	1,629	2.704	0.002430
137	Progress in Brain Research	7,582	2.680	0.008720
138	NEUROIMMUNOMODULATION	1,407	2.674	0.002020
139	PSYCHOPHYSIOLOGY	12,232	2.668	0.013530
140	NEUROLOGIC CLINICS	1,845	2.648	0.002980

141	Neuroscience Bulletin	1,204	2.624	0.003630
142	MUSCLE & NERVE	10,897	2.605	0.015990
143	STRESS-THE INTERNATIONAL JOURNAL ON THE BIOLOGY OF STRESS	2,051	2.590	0.004600
144	INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY	6,949	2.582	0.011480
145	NEUROCHEMICAL RESEARCH	8,300	2.581	0.011620
146	JOURNAL OF NEUROSCIENCE METHODS	14,651	2.554	0.017570
147	REVIEWS IN THE NEUROSCIENCES	1,572	2.546	0.003310
148	Journal of Parkinsons Disease	956	2.538	0.004240
149	RESTORATIVE NEUROLOGY AND NEUROSCIENCE	1,935	2.526	0.003460
150	Annual Review of Vision Science	59	2.522	0.000480
151	CHEMICAL SENSES	4,296	2.520	0.004140
152	CNS & Neurological Disorders-Drug Targets	2,447	2.506	0.005490
153	Frontiers in Neurorobotics	270	2.486	0.000750
153	NEUROPEPTIDES	1,873	2.486	0.002620
155	JOURNAL OF NEUROSCIENCE RESEARCH	12,794	2.481	0.009270
156	JARO-JOURNAL OF THE ASSOCIATION FOR RESEARCH IN OTOLARYNGOLOGY	2,000	2.455	0.004750
157	BEHAVIORAL NEUROSCIENCE	7,020	2.453	0.006230
158	SEIZURE-EUROPEAN JOURNAL OF EPILEPSY	4,289	2.448	0.008550
159	BRAIN AND LANGUAGE	6,186	2.439	0.009710
160	BRAIN AND COGNITION	6,424	2.432	0.008550
161	JOURNAL OF COMPARATIVE PHYSIOLOGY A-NEUROETHOLOGY SENSORY NEURAL AND BEHAVIORAL PHYSIOLOGY	5,156	2.429	0.005050
162	NEUROTOXICOLOGY AND TERATOLOGY	3,483	2.410	0.004070
163	JOURNAL OF NEUROPHYSIOLOGY	41,502	2.396	0.046140
164	JOURNAL OF NEURAL TRANSMISSION	6,198	2.392	0.008630
165	JOURNAL OF THE PERIPHERAL NERVOUS SYSTEM	1,484	2.361	0.002830
166	GAIT & POSTURE	11,367	2.347	0.016780
167	BMC NEUROSCIENCE	4,368	2.312	0.008820
168	CURRENT NEUROVASCULAR RESEARCH	907	2.298	0.001440
169	METABOLIC BRAIN DISEASE	2,033	2.297	0.003860
170	JOURNAL OF THE NEUROLOGICAL SCIENCES	15,454	2.295	0.021780
171	JOURNAL OF NEUROGENETICS	590	2.291	0.001490
172	NEUROPSYCHOLOGICAL REHABILITATION	1,662	2.280	0.002760
173	Social Neuroscience	1,427	2.255	0.003850
174	JOURNAL OF MOLECULAR NEUROSCIENCE	4,746	2.229	0.010260
175	AUTONOMIC NEUROSCIENCE-BASIC & CLINICAL	2,488	2.225	0.004430
176	BEHAVIOURAL PHARMACOLOGY	2,748	2.218	0.003490
177	Behavioral and Brain Functions	1,533	2.207	0.002370
178	JOURNAL OF THE INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY	5,824	2.181	0.008680
179	NEUROSCIENCE LETTERS	32,352	2.180	0.035070
180	CLINICAL EEG AND NEUROSCIENCE	869	2.163	0.001890
181	Brain and Behavior	919	2.157	0.004090
182	SYNAPSE	4,361	2.132	0.004260
183	Neural Development	907	2.077	0.002730
184	PSYCHIATRY AND CLINICAL NEUROSCIENCES	2,856	2.063	0.003630
185	NEUROSCIENCE RESEARCH	4,692	2.060	0.006060
186	INTERNATIONAL JOURNAL OF DEVELOPMENTAL NEUROSCIENCE	3,152	2.046	0.005030
187	Clinical Psychopharmacology and Neuroscience	329	2.000	0.001110

188	BRAIN INJURY	5,470	1.971	0.008430
188	VISION RESEARCH	15,982	1.971	0.013590
190	ACTA NEUROPSYCHIATRICA	570	1.939	0.001330
191	NEURAL COMPUTATION	9,746	1.938	0.006660
192	JOURNAL OF CHEMICAL NEUROANATOMY	2,008	1.925	0.002190
193	EXPERIMENTAL BRAIN RESEARCH	20,713	1.917	0.018910
194	BRAIN BEHAVIOR AND EVOLUTION	2,100	1.915	0.002280
195	Cognitive Neuroscience	390	1.870	0.001520
196	JOURNAL OF NEUROPSYCHIATRY AND CLINICAL NEUROSCIENCES	3,431	1.846	0.003320
197	HUMAN MOVEMENT SCIENCE	3,776	1.841	0.005900
198	Cognitive Neurodynamics	603	1.828	0.001140
199	Frontiers in Computational Neuroscience	1,714	1.821	0.008070
200	AUDIOLOGY AND NEURO-OTOLOGY	1,659	1.791	0.002780
201	NEUROPATHOLOGY	1,547	1.784	0.002910
202	Neural Regeneration Research	1,886	1.769	0.005290
203	NEUROLOGY INDIA	1,897	1.758	0.002200
204	INTERNATIONAL JOURNAL OF NEUROSCIENCE	2,967	1.750	0.003370
205	NEUROLOGICAL SCIENCES	3,949	1.749	0.008950
206	VISUAL NEUROSCIENCE	2,446	1.737	0.002520
207	ACTA NEUROLOGICA BELGICA	741	1.722	0.001380
208	BIOLOGICAL CYBERNETICS	4,499	1.716	0.002420
209	EUROPEAN NEUROLOGY	2,952	1.697	0.003420
210	STEREOTACTIC AND FUNCTIONAL NEUROSURGERY	1,412	1.692	0.001890
211	IEEE Transactions on Autonomous Mental Development	347	1.638	0.000680
212	NEUROPHYSIOLOGIE CLINIQUE-CLINICAL NEUROPHYSIOLOGY	1,116	1.593	0.001270
213	JOURNAL OF CLINICAL NEUROSCIENCE	6,485	1.557	0.013610
213	PSYCHIATRIC GENETICS	1,002	1.557	0.001600
215	Journal of Stroke & Cerebrovascular Diseases	3,864	1.517	0.012700
216	JOURNAL OF ELECTROMYOGRAPHY AND KINESIOLOGY	4,667	1.510	0.006220
217	NEUROPSYCHOBIOLOGY	2,540	1.491	0.002560
218	JOURNAL OF MUSCULOSKELETAL & NEURONAL INTERACTIONS	1,439	1.489	0.001970
219	JOURNAL OF COMPUTATIONAL NEUROSCIENCE	1,814	1.483	0.003420
220	Chemosensory Perception	317	1.474	0.000660
221	JOURNAL OF NEUROLINGUISTICS	976	1.403	0.001760
222	NEUROREPORT	13,876	1.395	0.006850
223	NEUROLOGICAL RESEARCH	3,415	1.376	0.004420
224	ACTAS ESPANOLAS DE PSIQUIATRIA	548	1.339	0.000690
225	JOURNAL OF MOTOR BEHAVIOR	1,955	1.327	0.001760
226	NEUROIMAGING CLINICS OF NORTH AMERICA	1,017	1.325	0.001350
227	CLINICAL AUTONOMIC RESEARCH	1,333	1.276	0.001630
228	JOURNAL OF CLINICAL NEUROPHYSIOLOGY	2,866	1.224	0.003190
229	Computational Intelligence and Neuroscience	1,320	1.215	0.005020
230	ACTA NEUROBIOLOGIAE EXPERIMENTALIS	1,173	1.207	0.001520
231	Cognitive Systems Research	492	1.182	0.000730
232	FOLIA NEUROPATHOLOGICA	611	1.093	0.000830
233	INVERTEBRATE NEUROSCIENCE	286	0.947	0.000280
234	Sleep and Biological Rhythms	436	0.926	0.000880
235	Translational Neuroscience	220	0.922	0.000830
236	NEUROENDOCRINOLOGY LETTERS	1,955	0.918	0.002300

237	SOMATOSENSORY AND MOTOR RESEARCH	823	0.909	0.000480
238	ARQUIVOS DE NEURO-PSIQUIATRIA	2,562	0.902	0.003310
239	JOURNAL OF VESTIBULAR RESEARCH-EQUILIBRIUM & ORIENTATION	816	0.900	0.001050
240	ACUPUNCTURE & ELECTRO-THERAPEUTICS RESEARCH	183	0.870	0.000080
241	Biologically Inspired Cognitive Architectures	161	0.753	0.000300
242	MOTOR CONTROL	637	0.750	0.000720
243	ENCEPHALE-REVUE DE PSYCHIATRIE CLINIQUE BIOLOGIQUE ET THERAPEUTIQUE	1,171	0.742	0.001000
244	JOURNAL OF PSYCHOPHYSIOLOGY	768	0.683	0.000680
245	Journal of Integrative Neuroscience	310	0.647	0.000480
246	Journal of the History of the Neurosciences	294	0.633	0.000410
247	Brain Impairment	276	0.600	0.000530
248	NeuroQuantology	259	0.586	0.000300
249	ARCHIVES ITALIENNES DE BIOLOGIE	581	0.580	0.001050
250	NETWORK-COMPUTATION IN NEURAL SYSTEMS	638	0.562	0.000240
251	NEUROCIRUGIA	285	0.548	0.000320
252	CESKA A SLOVENSKA NEUROLOGIE A NEUROCHIRURGIE	207	0.368	0.000190
253	Neurochemical Journal	121	0.340	0.000150
254	Ideggyogyaszati Szemle-Clinical Neuroscience	155	0.322	0.000280
255	ZHURNAL VYSSHEI NERVNOI DEYATELNOSTI IMENI I P PAVLOVA	216	0.236	0.000130
256	NEUROPHYSIOLOGY	169	0.207	0.000190
257	Journal of Neurological Sciences-Turkish	95	0.123	0.000190
258	IEEE Transactions on Cognitive and Developmental Systems	7	Not Available	0.000010

4. Druckexemplar der erfolgten Publikation

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Janina R. Behrens, Antje Kraft, Kerstin Irlbacher, Holger Gerhardt, Manuel C. Olma, Stephan A. Brandt

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Long-Lasting Enhancement of Visual Perception with Repetitive Noninvasive Transcranial Direct Current Stimulation

Janina R. Behrens[1,2], Antje Kraft[3], Kerstin Irlbacher[4], Holger Gerhardt[5], Manuel C. Olma[1†] and Stephan A. Brandt[1†]*

[1] Charité Universitätsmedizin Berlin, Berlin, Germany, [2] NeuroCare Clinical Research Center, Charité Universitätsmedizin Berlin, Berlin, Germany, [3] Department of Psychiatry, Psychiatric University Hospital St. Hedwig, Charité Universitätsmedizin Berlin, Berlin, Germany, [4] Medical care center, MVZ Reinickendorf Berlin, Berlin, Germany, [5] Center for Economics and Neuroscience, Rheinische Friedrich-Wilhelms-Universität Bonn, Bonn, Germany

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Tommaso Pizzorusso, Consiglio Nazionale Delle Ricerche (CNR), Italy

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Alexandre Esteves Medina, University of Maryland, Baltimore, United States
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***Correspondence:**
Janina R. Behrens
janina.behrens@charite.de

† These authors have contributed equally to this work.

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Understanding processes performed by an intact visual cortex as the basis for developing methods that enhance or restore visual perception is of great interest to both researchers and medical practitioners. Here, we explore whether contrast sensitivity, a main function of the primary visual cortex (V1), can be improved in healthy subjects by repetitive, noninvasive anodal transcranial direct current stimulation (tDCS). Contrast perception was measured via threshold perimetry directly before and after intervention (tDCS or sham stimulation) on each day over 5 consecutive days (24 subjects, double-blind study). tDCS improved contrast sensitivity from the second day onwards, with significant effects lasting 24 h. After the last stimulation on day 5, the anodal group showed a significantly greater improvement in contrast perception than the sham group (23 vs. 5%). We found significant long-term effects in only the central 2–4° of the visual field 4 weeks after the last stimulation. We suspect a combination of two factors contributes to these lasting effects. First, the V1 area that represents the central retina was located closer to the polarization electrode, resulting in higher current density. Second, the central visual field is represented by a larger cortical area relative to the peripheral visual field (cortical magnification). This is the first study showing that tDCS over V1 enhances contrast perception in healthy subjects for several weeks. This study contributes to the investigation of the causal relationship between the external modulation of neuronal membrane potential and behavior (in our case, visual perception). Because the vast majority of human studies only show temporary effects after single tDCS sessions targeting the visual system, our study underpins the potential for lasting effects of repetitive tDCS-induced modulation of neuronal excitability.

Keywords: contrast sensitivity, noninvasive brain stimulation, plasticity, transcranial direct current stimulation, visual perceptual learning, primary visual cortex

INTRODUCTION

Sensitivity to contrast is crucial, not only for vision at dusk and nighttime (Brabyn et al., 2005), but also in daylight, e.g., while reading. The processing of visual contrast is one of the main functions of the primary visual cortex (V1; Foster et al., 1985; Mullen et al., 2010), which plays a key role in humans' faculty to visually process their environment. V1 receives input from the retina via the optic nerve, processes visual perceptual information, and is the basis for further integration of visual information in higher visual and nonvisual areas (Fahle, 2004; Schummers et al., 2005). While the functions of V1 are relatively well understood, the degree of plasticity of the human visual cortex is still largely unclear. Exploring the neuroplastic capacity of V1 in the intact human brain may help us understand its ability to recover from damage.

Given the increasing average life expectancy of large parts of the world's population and the fact that stroke occurs more frequently in the elderly (Feigin et al., 2014), often affecting the visual cortex, potential treatments with the aim of rehabilitating the visual system are needed.

Previous studies have shown that the neuronal configuration of visual cortices can be altered by repeatedly performing visual tasks. Training on such tasks has been demonstrated to lead to a short-term or permanent improvement of vision: Several animal studies provide evidence that visual perceptual learning (PL) is associated with a change of local neuronal inhibition and excitation networks within V1 layers, which occurs under modulation from higher brain cortices (top-down) and vice versa (bottom-up; for an overview see Foster et al., 1985; Schummers et al., 2005).

In humans, Sowden et al. (2002) observed that improved contrast perception in a sinusoidal luminance gratings task prevailed for 6 months after extensive practice. Similarly, functional magnetic resonance imaging (fMRI) studies have shown that several weeks of training in a texture discrimination task (Yotsumoto et al., 2008) or in low-contrast oriented patterns (Furmanski et al., 2004) led to improved task performance that was paralleled by an enhanced blood oxygen level-dependent (BOLD) signal in V1, indicating neuronal plasticity in progress (Maertens and Pollmann, 2005).

Together, these studies provide evidence for the neuroplasticity of human V1. However, from a therapeutic perspective, the applicability of extensive training to induce learning processes as mentioned above is limited because they are very time-consuming and demanding for the patient. Therefore, exploration of the lasting effects of brain stimulation has the potential to provide a basis for the development of a practical and time-saving therapeutic tool that enhances visual performance in patients.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique (NIBS) that has comparable effects to those of rhythmic stimulation techniques (Lang et al., 2007). For instance, in a study by Clavagnier et al. (2013), continuous theta burst stimulation of the visual cortex temporarily improved contrast sensitivity in adults with amblyopia. A previous tDCS study by Antal et al. (2004) showed a change in the time to the N70 peak of the primary visual evoked potential (VEP), indicating tDCS-induced changes related to oscillatory activity.

Plow et al. (2011, 2012) applied anodal tDCS to patients with stroke concurrent to vision restoration therapy (VRT) and observed superior expansion of the visual field compared to VRT alone. Olma et al. (2013) found that patients with stroke with occipital lesions showed improved motion perception (a function attributed to V5) after anodal tDCS over the unimpaired V1, which was still measurable up to 28 days later.

A channel through which tDCS possibly works is that tDCS could improve visual perception by enhancing the previously described inert neuronal plasticity of V1. Regarding the level of individual neurons, it is possible that immediate tDCS effects are generated by the modulation of cortical activity in neocortex cells through shifting the resting membrane potential (for an overview see Nitsche et al., 2008). Longer-term effects of repeated tDCS might result from synaptic strengthening that is triggered by the increased short-term activity and that is similar to the consolidation of learned visual performance (for an overview see Sale et al., 2011). Thus, on a cellular level, both the consolidation of learned visual performance (Sale et al., 2011) and tDCS (Nitsche et al., 2008) involve long-term potentiation-dependent synaptic strengthening.

Until now, studies that investigated the effects of single tDCS application in the visual system showed only weak tDCS effects compared to other brain areas (for an overview, see Antal et al., 2011).

We here investigate the hypothesis that repetitive application of anodal tDCS to the visual cortex changes contrast perception in healthy subjects. This poses a challenge in that it requires improving an already physiologically intact working visual system. In contrast to previous studies, we investigate long-term effects that result from repeated tDCS application alone, without any concurrent training in a psychophysical, behavioral task. More specifically, this study investigates whether it is possible to boost contrast perception in healthy subjects for an extended period of time. This, in turn, could serve as a basis for further clinical research regarding the plasticity of this area.

METHODS

General Setup

We applied anodal tDCS or sham stimulation for 20 min on 5 consecutive days to V1 of 12 randomly chosen subjects (anodal group) and 12 control subjects (control group), respectively (**Figure 1**). High contrast sensitivity is defined as the ability to detect even minor differences in the luminance of visual input. Contrast sensitivity in different parts of the human visual field can be measured by automated, computer-based threshold perimetry, which measures contrast sensitivity in decibels (dB). Small dots of light of varying luminance were presented repeatedly on an isoluminous background at different locations within the central 10° of the visual field. When applying this method, improved contrast sensitivity is characterized by a decrease in the stimulus luminance that is necessary for the presented stimuli to be just above the detection threshold, given the background luminance.

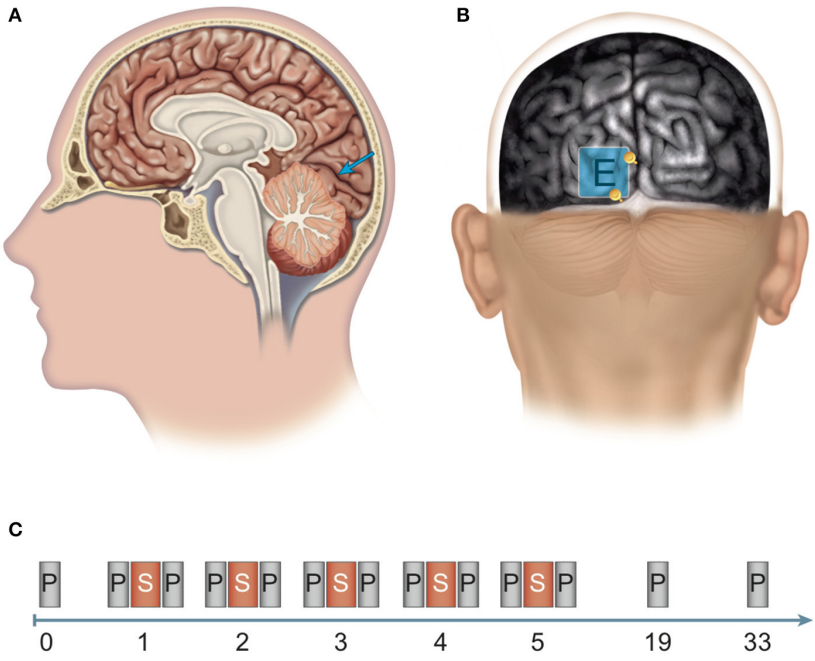

FIGURE 1 | Site of stimulation and experimental design. **(A, B)** Determination of the position of the polarization electrode: An anatomical magnetic resonance image (MRI) was aligned to the surface using the Nexstim system for MRI-guided brain stimulation. **(A)** The target region for anodal stimulation was the left-hemispherical striate area (V1, blue arrow). **(B)** The polarization electrode (E) was placed over the target region and between two anatomical structures (see yellow depth markers): laterally, the inter-hemispherical fissure, and caudally, the boundary between the occipital cortex and the cerebellum (cerebellar tentorium). **(C)** Experimental design: Pre-test before the experiment (0). Stimulation phase: Over five consecutive days (days 1–5), subjects received brain stimulation (S) via anodal transcranial direct current stimulation (tDCS) or sham stimulation and participated in computerized threshold perimetry tests before and after stimulation. Follow-up measurements: Computerized threshold perimetry measurements were taken 2 and 4 weeks (days 19 and 33, respectively) after the final stimulation. $N = 24$ healthy subjects (12 sham group, 12 anodal group).

Subjects and Design

Twenty-four healthy, right-handed subjects with a mean age of 24.5 years ($SD = 3.53$) participated. All subjects provided written informed consent prior to their participation in the study. The 24 subjects were randomly assigned to the anodal tDCS group or to the control group. Because of a possible gender-specific difference in modulatory effects of anodal tDCS on V1 (Chaieb et al., 2008), our experiment comprised 12 women and 12 men and a homogeneous distribution of 6 women and 6 men in each group. Included were subjects with normal or corrected-to-normal visual acuity and no known neurological, psychiatric, or ophthalmic impairments. We used a double-blind, sham-controlled, between-subjects design. The study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin in conformity with the tenets of the Declaration of Helsinki. At the end of our experiment, all subjects were paid for their participation.

Stimulation Technique and Procedure

tDCS was delivered by a battery-driven DC-stimulator (DC-STIMULATOR PLUS, NeuroConn GmbH, Ilmenau, Germany). We chose the electrode position based on electrode positions of previous tDCS studies on the visual system (Antal et al., 2011) that had proven suitable in our laboratory (Kraft et al., 2010). The reference electrode (size: 7 × 5 cm) was placed on the middle of the skullcap, i.e., at position Cz. It has been shown that binocular viewing may impair the effects of NIBS on a visual perceptual task (Saint-Amour et al., 2005). This might be explained by providing a more robust cortical representation of the visual stimuli (Meese et al., 2006). Therefore, our participants viewed the stimuli monocularly with a patch over their nondominant (left) eye.

The occiput side was randomly chosen (left occiput). To facilitate group analysis, we consistently applied tDCS to the chosen (left) visual cortex of all subjects. To ensure accurate placement of the polarization electrode, positioning was guided by using T_1-weighted magnetic resonance (MR) imaging (MP-RAGE sequence, TR/TE = 10/4 ms, FA = 12°, TI = 100 ms, voxel size = 1 × 1 × 1 mm^3). The MR image was acquired with a 1.5-Tesla MAGNETOM Vision MR scanner (Siemens, Erlangen, Germany). The MRI data were aligned to the scalp via the navigated brain stimulation system eXimia NBS System 3.0 (Nexstim Germany GmbH, Frankfurt, Germany). We placed the middle of the electrode over the striate area of the primary visual cortex of the left hemisphere (see **Figure 1**).

tDCS has been shown to be a safe method, and it is suitable for double-blind experimental protocols (Gandiga et al., 2006). Conforming to current safety guidelines and recommendations (Poreisz et al., 2007), both electrodes were applied in saline-soaked synthetic sponges in order to reduce impedance. Electrodes were fixed on subjects' heads with self-adhesive bandages. Subjects received anodal tDCS (1.5 mA, current density: 0.06 mA/cm^2) or placebo (sham) stimulation of the left visual cortex for 20 min on 5 consecutive days. The stimulation protocol featured automatic ramping at both the beginning and the end of the stimulation for 15 s. The sham stimulation procedure was identical, but current application was automatically limited to ramping times. This ensured that subjects could not distinguish real from sham stimulation. This method was utilized in previous studies from our laboratory (Kraft et al., 2010).

Measurement of Contrast Sensitivity

Before and immediately after stimulation, contrast sensitivity of subjects was measured using computerized threshold perimetry (Humphrey Field Analyzer II, Carl Zeiss Meditec, Inc., Dublin, CA). The measurements were performed using a 10-2 strategy, i.e., including the central 10° of the visual field in steps of 2° [Swedish Interactive Threshold Algorithm (SITA)] (Bengtsson et al., 1997). During measurement, subjects were seated in a dark room at a distance of 30 cm to the presented light stimuli. Stimuli were shown with varying luminance for 200 ms (stimulus size: Goldmann III; constant background illumination: 10 cd/m^2). Subjects had to push a button every time they detected a light stimulus. They received no feedback and had been accustomed to the measurement procedure before participating in the experiment. All measurements were made under fixation control. At the end of each measurement, the stimulus threshold was calculated for 68 visual field positions within the central 10° of the visual field of the right eye (the left eye was covered).

To evaluate potential long-lasting effects, subjects completed the 10-2 threshold perimetry measurement at two follow-up dates (no tDCS application), 2 (day 19) and 4 weeks (day 33) after the last day of stimulation (day 5; see **Figure 1**).

Analysis and Statistics

Statistical analysis was performed using SPSS, version 19 (IBM Corp., Armonk, NY). An analysis of variance (ANOVA) with repeated measures was performed to investigate tDCS effects during the stimulation phase (days 1–5) and follow-up dates (days 19 and 33). Our hypothesis was that anodal tDCS would enhance contrast sensitivity (measured as higher dB) compared to sham stimulation over the stimulation phase. Therefore, the independent variable was tDCS stimulation (between-subject factor *stimulation*). The within-subject factors were (a) the effect between before and after stimulation, defined as *intervention*, (b) the development over time (factor *time*) and (c) the degrees of the visual field, defined as *eccentricity*. Subsequent exploratory tests (ANOVAs and unpaired *t*-tests) were performed exploratively (no α correction) to analyze the pattern of the development of contrast sensitivity of all subjects (anodal and sham stimulation). The Greenhouse–Geisser correction was applied when appropriate. All tests were two-tailed, and significance for all effects was assumed when $P < 0.05$. Contrast sensitivity was the dependent variable in all analyses.

RESULTS

Repeated Anodal tDCS Improves Contrast Sensitivity

The main finding of our analysis is that compared to sham, the anodal group showed a significantly greater enhancement of contrast perception (**Figure 2**; days 1–5, $P = 0.037$). Although we observed enhancement of contrast perception across both groups, it was not significant in the sham group ($P = 0.066$).

Regarding the development at single days as a comparison from baseline (as day 1 pre stimulation) to days 1–5 post-stimulation (**Figure 3**), the anodal group showed a significantly greater enhancement of contrast perception (compared to sham) from day 2 to 5 ($P < 0.050$).

Contrast Perception Remains High 24 h after tDCS Stimulation

This analysis revealed that contrast perception increased more between days for the anodal group than for the sham group. Average 24-h effects (d*n*pre − d(*n*−1)pre) were significantly greater in the anodal group, compared to sham (between-subject stimulation: $F = 6.332$, $P = 0.020$).

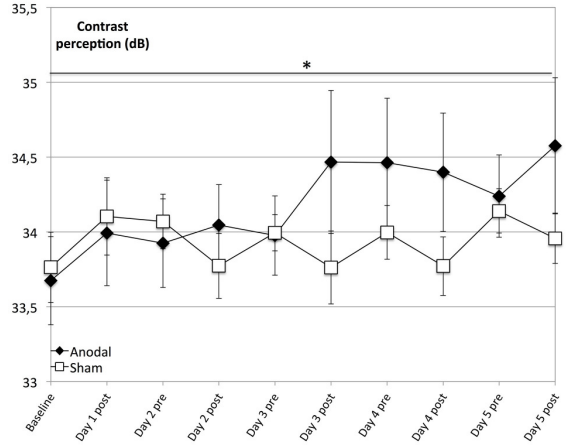

FIGURE 2 | Effects of anodal and sham tDCS on 5 consecutive days. Contrast perception improved across both groups and was not significant in the control group (rectangle line; within-subject effect *time*: $F = 2.782$, $P = 0.066$). Effects were greater for the anodal group (diamond line; interaction of within-subject effect *intervention* and between-subject effect *stimulation*: $F = 6.456$, $P = 0.019$), with a significantly greater average increase in performance over time (days 1–5, interaction of within-subject effect *time* and between-subject effect *stimulation*: $F = 2.237$, $P = 0.037$). *$P < 0.05$, error bars show standard error of the mean (SEM). $N = 24$ healthy subjects (12 sham group, 12 anodal group).

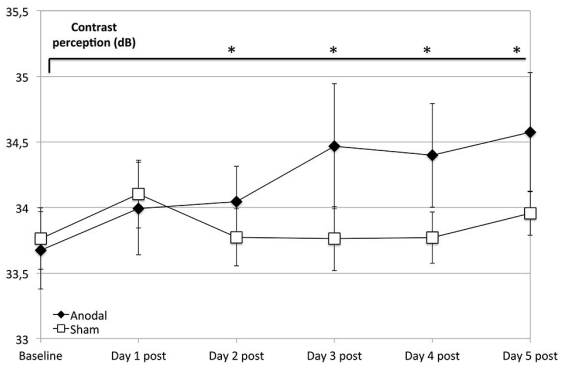

FIGURE 3 | Effects of anodal and sham tDCS at 5 consecutive days after stimulation. Compared to the control group (rectangle line), effects of stimulation were greater for the anodal group at days 2–5 compared to baseline (ANOVA days 1–33, days 19 and 33 are not shown) diamond line; contrasts of within-subject effect *time* and between-subject effect *stimulation*: day 2: $F = 4.659$, $P = 0.042$; day 3: $F = 9.293$, $P = 0.006$; day 4: $F = 6.972$, $P = 0.015$; day 5: $F = 6.332$, $P = 0.020$). *$P < 0.05$, error bars show standard error of the mean (SEM). $N = 24$ healthy subjects (12 sham group, 12 anodal group).

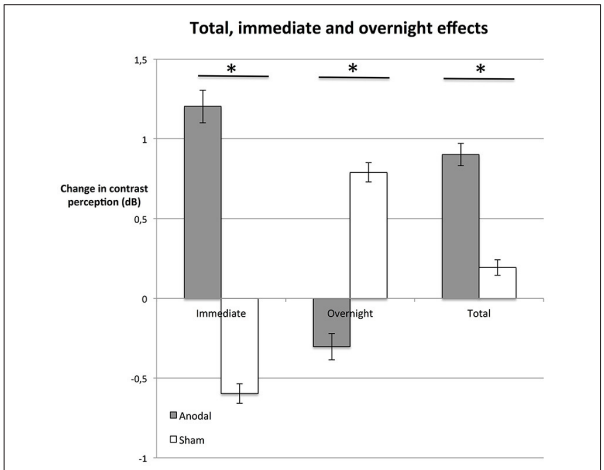

FIGURE 4 | Immediate, overnight, and total effects. The average difference between performance immediately after stimulation and right before simulation (immediate, d*n*post compared to d*n*pre, left bars), were greater in the anodal group (gray bars; $P = 0.015$). In contrast, effects between days (overnight, d*n*pre compared to d($n-1$)post, central bars) were greater in the sham group (white bars; $P = 0.034$). Total enhancement of contrast perception (total, right bars) at day 5 (post), compared to baseline was superior on average ($P = 0.047$) in the anodal group than in sham. *$P < 0.05$; error bars show SEM. $N = 24$ healthy subjects (12 sham group, 12 anodal group).

tDCS Effects are Based on Significantly Greater Immediate Enhancement

At the last day, the average total enhancement from baseline to day 5 post-stimulation was 0.9 dB in the anodal group (**Figure 4**); in other words, stimuli presented on day 5 could be detected at a 23% weaker luminance compared to stimuli presented at the beginning of the experiment (baseline). In the sham group, contrast sensitivity was enhanced by 0.2 dB (i.e., 5% weaker stimulus luminance).

We investigated whether these effects were based on enhancement immediately after stimulation (immediate effect, d*n*post−d*n*pre) or if there was an additional enhancement between days, such that subjects started at a higher contrast sensitivity level after a night of rest (overnight effect, d*n*pre−d($n-1$)post; **Figure 4**).

The average difference between performance immediately after stimulation and right before simulation was greater in the anodal group (**Figure 4**; unpaired Student's *t*-test: $P = 0.015$). In fact, in the control group, the immediate effect of receiving the sham stimulation was a decrease in contrast sensitivity (see **Figure 4**). We interpret this as a fatigue effect, i.e., subjects became tired as a consequence of the procedure (Flammer and Niesel, 1984). If this is the case, tDCS not only counteracted the fatigue effect, but the stimulation duration and strength of tDCS was powerful enough to induce a positive immediate effect. The difference in total improvement (day 5 post-stimulation compared to baseline) between the anodal group and the sham group was significant (unpaired Student's *t*-test: $P = 0.047$, see **Figure 4**).

tDCS-induced enhancement of consolidation overnight has been observed previously (Brasil-Neto, 2012). Our analysis reveals a contrasting pattern between the two groups (**Figure 4**). Total enhancement of the anodal group was mainly based on immediate effects (unpaired Student's *t*-test: $P = 0.015$). Between days (overnight), performance of subjects in the anodal group regressed to a level below the post-stimulation level of the previous day. In contrast, overnight effects were significantly greater in the control group than in the anodal group (unpaired Student's *t*-test: $P = 0.034$): the sham group started at a slightly higher level pre-stimulation than post-stimulation the previous day. This suggests that subjects recovered overnight from the observed fatigue effect.

Follow-up Measurements after 2 and 4 Weeks Reveal Long-Lasting Effects within the Central Visual Field

We did not find a significant enhancement in contrast perception at the follow-up measurements compared to baseline regarding the whole visual field (degrees 2–10) across all subjects ($P = 0.156$) or between groups ($P = 0.312$). However, the anodal group showed an improved performance compared to that of the sham group over the whole visual field (degrees 2–10) and over the study's time span that was not significant ($P = 0.076$; **Figure 5**).

Interestingly, on follow-up dates, the tDCS-induced enhancement of contrast perception was solely significant within the central visual field (degrees 2–4, day 19 to baseline, $P = 0.013$ and day 33 to baseline, $P = 0.021$), whereas there was no significant interaction regarding the peripheral visual field (day 19 to baseline, $F = 2.555$, $P = 0.124$ and day 33 to baseline, $F = 2.341$, $P = 0.140$; **Figure 6**).

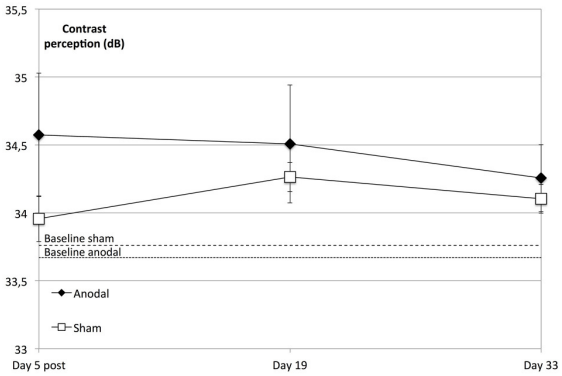

FIGURE 5 | tDCS effects at follow-up dates. The enhancement in contrast perception at the follow-up measurements compared to baseline was not significant regarding the whole visual field (degrees 2–10) across all subjects (within-subject effect *time*: $F = 1.798$; $P = 0.156$) or between groups (between-subject effect *stimulation*: $F = 1.073$, $P = 0.312$). Over the study period and compared to the sham group (rectangle line), the anodal group (diamond line) showed no significant improvement of contrast sensitivity (interaction of within-subject effect *time* and between-subject effect *stimulation*: $F = 2.390$; $P = 0.076$). Compared to sham, tDCS-induced significant enhancement of contrast sensitivity (day 5 post) did not lead to a sharper decline on follow-up dates ($t = 5$, 19, 33; between-subject effect *stimulation*: $F = 0.089$, $P = 0.768$, within-subject effects *time*: $F = 1.972$, $P = 0.151$ and *interaction time* × *stimulation*: $F = 0.244$, $P = 0.797$). Baseline levels are the dotted (anodal) and dashed (sham) lines. Error bars show SEM. $N = 24$ healthy subjects (12 sham group, 12 anodal group).

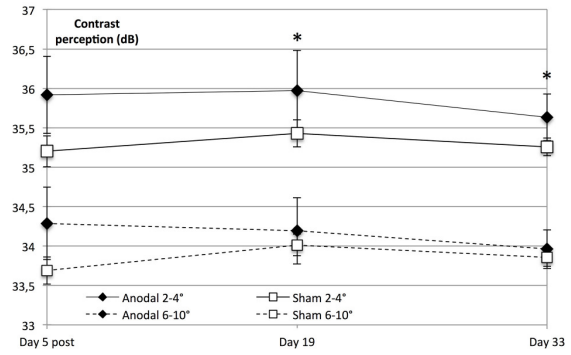

FIGURE 6 | Significant lasting effect in the central visual field. Contrast sensitivity in the central visual field was significantly higher than peripheral sensitivity in both groups (within-subject effect *eccentricity*: $F = 262.494$, $P < 0.001$). Contrast perception on follow-up dates revealed that tDCS-induced enhancement of contrast perception was solely significant within the central visual field (anodal 2–4°; diamond line) on day 19 compared to baseline (degrees 2–4; *eccentricity* × *stimulation* × *time* day 19 to baseline: $F = 7.338$, $P = 0.013$) and day 33 compared to baseline ($F = 6.144$, $P = 0.021$), whereas there was no significant effect regarding the visual field as a whole (*stimulation* × *time* day 19 to baseline: $F = 2.558$, $P = 0.124$, and day 33 to baseline: $F = 2.325$, $P = 0.140$). *$P < 0.05$; error bars show SEM. $N = 24$ healthy subjects (12 sham group, 12 anodal group).

Because of the retinotopic organization of V1, we considered it possible that tDCS had differential effects depending on eccentricity. We therefore investigated whether the enhancement of contrast sensitivity was spatially homogeneous within the examined visual field (10°). To this end, we compared central (2–4°) with peripheral (6–10°). We found that central visual contrast sensitivity was significantly higher than peripheral sensitivity in both groups ($P < 0.001$).

A repeated-measures ANOVA was performed to compare the development at the follow-up dates, revealing that the tDCS-boosted enhancement of contrast perception did not lead to significant differential decline of contrast perception after the stimulation period compared to that in the control group (day 5 post to days 19 and 33, $P = 0.797$; **Figure 5**).

DISCUSSION

This study is the first to provide evidence that anodal tDCS over the primary visual cortex induces long-lasting enhancement of contrast perception. We focused on the physiologically intact system of healthy subjects and showed that the degree of tDCS-induced improvement of contrast perception within 5 days was comparable in magnitude to the age-related decline of contrast perception over the course of 7 years (Hahn et al., 2009). Until now, it was unclear whether anodal tDCS could at all improve visual function.

Despite the popularity of tDCS in many areas of neuroscience, relatively few studies have investigated tDCS effects on the visual cortex (Antal et al., 2011; Olma et al., 2013) and, in contrast to stimulation of the motor cortex, tDCS application over the visual cortex has not been shown to induce comparable effects (Antal et al., 2001; Lang et al., 2007). Effects sustained beyond the end of the stimulation were limited to 15 min following 10 min of anodal tDCS of the visual areas, whereas 10 min of anodal tDCS over the motor cortex was able to induce sustained cortical excitability for up to 60 min (Nitsche and Paulus, 2001).

It is likely that the varying anatomical conditions are one reason for different tDCS effects. Because skull thickness determines the flow of current through the brain and thus the strength of tDCS effects (Datta et al., 2011; Giordano et al., 2017), one plausible reason for smaller tDCS effects over V1 compared to M1 can be seen in the relatively greater skull thickness and density of the occipital bone compared to the parietal bone (Voie et al., 2014; Zarghooni et al., 2016). The tDCS effects are also dependent on the distance and orientation of neuronal axons to the electrode (Paulus, 2003): the drift of membrane potential is higher and the tDCS effect more intense when current flow directs longitudinal to the neuronal axons, like in M1, than cross the axons (Nitsche et al., 2008). In contrast to M1, the V1 cells are mainly horizontally orientated and located deep in the occipital cortex (Dougherty et al., 2003). Thus, this aspect could be another reason for relatively weaker tDCS effects over V1.

In contrast to the discussed previous studies that showed only weak anodal tDCS effects on V1, our study substantiates the notion that tDCS over V1 induces long-lasting effects. We saw the first significant differences between anodal and sham group after the second stimulation (baseline to days 2–5 post-stimulation,

see **Figure 3**). Thus, in contrast to M1, tDCS effects on V1 seem to be highly dependent on certain conditions, like a longer stimulation duration and repetitive tDCS application to overcome the anatomical barriers discussed above.

Contrast sensitivity significantly increased from baseline to day 5, demonstrating that subjects of the anodal group were able to detect darker luminance points with an average of 23% reduced stimulus luminance, compared to only 5% in the sham group. These findings indicate that tDCS was able to enhance the processing that is performed by a physiologically intact primary visual cortex.

To assess the size of the effect that we were able to induce via tDCS, let us compare our results with a perimetry study by Hahn et al. (2009). Hahn et al. investigated the extent to which there is an age-related decrease in contrast sensitivity in healthy subjects. Focusing on the central 8° of the visual field, they observed a linear age-related decline in contrast perception in healthy subjects starting at the age of 41 years. The improved contrast perception that we observed as a result of 5 days of anodal tDCS is comparable in magnitude to the age-related decline in contrast perception over the course of 7 years in healthy subjects. It is important to note that the decline in contrast sensitivity that Hahn et al. observed does not seem to be caused by age-dependent contrast processing in V1 but rather by age-induced impairment of the rod cells in the human retina. Still, our results suggest that it might be possible to at least partially offset this age-related loss of contrast sensitivity via noninvasive brain stimulation, since we only manipulated V1 activity and not rod cells.

We did not detect any tDCS-boosted consolidation overnight (i.e., in average $d(n+1)\text{pre} \leq dn\text{post}$). This finding is in line with the results of a recently published study by Peters et al. (2013), which differ from the findings of other studies that investigated tDCS-induced overnight effects for different types of learning. One explanation might be that resting or sleep has been established to be beneficial particularly when human awareness is required and during declarative and procedural skill learning (Walker and Stickgold, 2004; Brown et al., 2009; Debarnot et al., 2009; Kandel, 2009; Doyon et al., 2011), while our relatively simple perimetry task predominantly requires implicit learning. Hence, an effect of sleep may be weak.

Importantly, our findings show that long-term tDCS effects were only significant within the central visual field—the retinal region with the highest contrast sensitivity (Skrandies, 1985). It is likely that tDCS-induced plasticity caused the improvement of vision and is responsible for the lasting enhancement of contrast perception within this visual field. Over the stimulation time (days 1–5), there was no differential enhancement of contrast perception between central and peripheral fields.

We argue that basic anatomical and structural conditions underly the long-term enhanced visual performance observed in this study. First, due to the topographic representation of the visual field in V1, the central visual field maps to the occipital pole and the adjacent brain area (i.e., areas close to the polarization electrode), while the parts of V1 that process the peripheral field run across the calcarine fissure in the depth of the brain (i.e., farther away from the polarization electrode; Horton and Hoyt, 1991). Consequently, compared to the brain regions that represent the peripheral field, a higher current density reaches the occipital brain region, possibly facilitating the synaptic strengthening within this region.

Second, relative to the peripheral visual field, a larger cortical area represents the central visual field in the cortex (Horton and Hoyt, 1991; Spillmann, 2014). The linear extent of the striate cortex to which each degree of the retinal visual field projects is called the magnification factor (Spillmann, 2014). In a positron emission tomography (PET) study (Fox et al., 1987), the magnification factor was investigated in the human striate cortex. Fox et al. (1987) observed that the neuronal response rate (i.e., the cerebral blood flow per mm) was higher for the central field, i.e., within the macular (0.1–1.5° with 3.4 mm/degree) and peri-macular region (up to 5.5° with 1.6 mm/degree) than for the peripheral field (5.5–15.5° with 0.9 mm/degree). Thus, in addition to the relatively higher current density reaching the areas that process the central 2–4 degrees of the visual field, these areas may be more susceptible to tDCS than are those representing the peripheral 6–10 degrees.

A potential explanation for the enhanced visual contrast perception that we observe is therefore that anodal tDCS triggers processes that alter the synaptic configuration within the visual cortex. This would be consistent with evidence that tDCS-induced long-term effects require LTP-dependent synaptic strengthening, as observed in studies using animal models (using direct current stimulation: Bindman et al., 1962; Creutzfeldt et al., 1962; Ranieri et al., 2012) as well in humans (for an overview, see Kim et al., 2010).

The underlying molecular mechanisms of tDCS-induced effects, especially following *repeated* tDCS application, appear similar to the innate learning processes of the visual cortex. These processes involve increased activation of NMDA receptors and higher concentration of BDNF (Fritsch et al., 2010; Kim et al., 2010), and they seem to be similar to the synaptic strengthening that gives rise to the consolidation of learned visual performance (for an overview, see Plow et al., 2012).

Interestingly, averaged across all subjects, there was a constant enhancement of contrast perception over the subsequent days (1–5), which might be the consequence of habituation to the test known to occur in repeated automated perimetry testing that follows the SITA standard (Yenice and Temel, 2005). Importantly, the enhancement of the control group over time was not significant. In contrast, subjects in the anodal group started, on average, on a significantly higher level of visual performance on following days (days 1–5), as evident from the significantly positive 24-h tDCS effects (**Figure 2**).

In this regard one could consider that tDCS enhances the experience-dependent plasticity that was observed in animal (DCS) studies (Cooke and Bliss, 2006; Cooke and Bear, 2010). These animal and also human (Frenkel et al., 2006) studies indicate that V1 plasticity is stimulus-specific. Like in these studies, we presented identical visual stimuli each day. Thus, it is possible that the daily presentation of the stimuli evoked a stimulus-specific response potentiation (SRP) in all subjects and

that SRP was enhanced by daily anodal tDCS. To further address this hypothesis, tests with different stimuli would be necessary.

tDCS-induced performance enhancement from day 1 to day 5 did not lead to a steep reduction of contrast perception over the follow-up time points (days 19 and 33). However, testing performance of the anodal group peaked on the last day of the stimulation period (day 5 post). That is, while the anodal group showed superior performance on follow-up dates, contrast sensitivity decreased over those 2 weeks without tDCS application. In this regard, tDCS did not enhance consolidation processes once the stimulation block had ended.

Together, the findings of this study showed that tDCS improves visual perceptual performance directly after stimulation for about 24 h and up to a month later within the central visual field. Regarding these values as a first indicator for the time span over which an effect can be expected in the therapeutic application of tDCS to patients, our result suggests that it would be necessary to repeat tDCS application periodically.

As in a recently published study of Brückner and Kammer (2016), previous tDCS studies showed high inter-individual variability in the response to tDCS applied over the visual cortex. Given the high anatomic variability of the visual cortex in relation to the skull (Stensaas et al., 1974; Dougherty et al., 2003), the approach of referencing the stimulation electrode with the skull-based standard 10/20 EEG system (Brückner and Kammer, 2016) seems questionable but is widely used. In a recently published review about tDCS use within the sensory perceptual processing areas (Costa et al., 2015), only 6% of all 82 listed studies used an exact electrode position via MRI (3%) or transcranial magnetic stimulation (3%). However, it is likely that we were able to show long-lasting tDCS effects because we used MRI navigation to localize the individually optimal position directly over the calcarine sulcus.

CONCLUSION

In sum, given the lack of previous studies investigating repeated tDCS application in the visual system of healthy controls, we provide novel insights by demonstrating long-lasting effects of tDCS over V1. In contrast to the majority of previous studies, we used a more precise method to determine the location of the polarization electrode on the surface using individual MRI data and navigation software. We attribute the observation of long-lasting effects to this method and the repetitive tDCS application. In contrast to short-lasting effects, long-lasting effects indicate plasticity. In this way, our results suggest that repetitive tDCS over V1 may be a promising neurorehabilitation tool for patients with chronic visual disability occurring after stroke. Importantly, the tDCS effects demonstrated by our study did not require an extensive, time-consuming, and effortful simultaneous visual training paradigm, such as VRT. This offers an important advantage in the development of rehabilitation programs for older patients who are more severely affected by diseases.

AUTHOR CONTRIBUTIONS

JB, MO, AK, KI, and SB designed research. JB performed research. JB, MO, HG, AK, and SB analyzed the data. JB wrote the work. MO, HG, AK, KI, and SB critically revised the work, agreed to be accountable for all aspects of ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and gave final approval of the version to be published

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6. Publikationsliste

Dissertation: Erst- und Co-Autorenschaft bei tDCS-Studien:

Janina R. Behrens, Antje Kraft, Kerstin Irlbacher, Holger Gerhardt, Manuel C. Olma, Stephan A. Brandt, Long-lasting enhancement of visual perception with repetitive noninvasive transcranial direct current stimulation, Frontiers in Cellular Neuroscience, 2017

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Kongressbeiträge:

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1) Deutschen Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung (DGKN) 2011, Münster, Deutschland

Posterpräsentation: Janina R. Behrens, Antje Kraft, Kerstin Irlbacher, Holger Gerhardt, Manuel C. Olma, Stephan A. Brandt, Brandt, Does repetitive anodal tDCS applied on the visual cortex induce long-term improvements in visual contrast perception?

2) ECTRIMS 2013, Kopenhagen, Dänemark

Posterpräsentation: Behrens J, Pfüller C, Mansow-Model S, Otte K, Paul F, Brandt AU, Microsoft Kinect-based gait analysis in multiple sclerosis patients.

3) American Academy of Neurology 2014 Annual Meeting, Philadelphia, USA

Posterpräsentationen: Janina R. Behrens, Sebastian Mertens, Karen Otte, Sebastian Mansow-Model, Friedemann Paul, Alexander U. Brandt, Kinect-based gait analysis in patients with multiple sclerosis.

4) MSBOSTON, Joint ACTRIMS-ECTRIMS Meeting 2014, Boston, USA

Vortrag: Janina R. Behrens, Sebastian Mertens, Karen Otte, Sebastian Mansow-Model, Friedemann Paul, Alexander U. Brandt, Postural control analysis in multiple sclerosis with perceptive computing based on Microsoft's Kinect.

Posterpräsentation: Janina R. Behrens, Tim Sinnecker, Joseph Kuchling, Lutz Harms, Klemens Ruprecht, Thoralf Niendorf, Jan Dörr, Friedemann Paul, Jens Würfel, Perivascular inflammation in Baló's concentric sclerosis — preliminary results from a 7T MRI study.

5) American Academy of Neurology 2015 Annual Meeting, Washington, USA

Posterpräsentation: Janina R. Behrens, Sebastian Mertens, Karen Otte, Sebastian Mansow-Model, Friedemann Paul, Alexander U. Brandt, Development of a comprehensive motor function assessment battery for multiple sclerosis using perceptive computing.

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6. Fortsetzung Publikationsliste

Kongressbeiträge:

5) American Academy of Neurology 2015 Annual Meeting, Washington, USA

Posterpräsentation: Janina Behrens, Friedemann Paul, Klemens Ruprecht, Jan Dörr, Low 25-hydroxyvitamin D, but not bioavailable vitamin D levels are a risk for multiple sclerosis.

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