Aus der Klinik und Poliklinik für Psychiatrie und Psychotherapie
der Ludwig-Maximilians-Universität München
Direktor: Prof. Dr. med. H.-J. Möller

Der Einfluss von präfrontaler transkranieller Gleichstromstimulation (tDCS) auf EEG- und fMRT-Ruhenetzwerke

Dissertation
zum Erwerb des Doktorgrades der Humanbiologie
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

vorgelegt von
Daniel Keeser
aus München

2012

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Berichterstatter:	Priv. Doz. Dr. med. Frank Padberg
Mitberichterstatter:	Priv. Doz. Dr. med. Angela Deutschländer
	Prof. Dr. med. Michael Strupp
	Priv. Doz. Dr. med. Jennifer Linn
Mitbetreuung durch den promovierten Mitarbeiter:	Prof. Dr. med. Christoph Mulert
Dekan:	Prof. Dr. med. Dr. h.c. M. Reiser, FACR, FRCR
Tag der mündlichen Prüfung:	16.07.2012

Für Phil-Marcel

Zusammenfassung

Das Hauptziel der vorliegenden Dissertation war die Untersuchung des Einflusses der präfrontalen Gleichstromstimulation (tDCS) auf die Modulation kortikaler Netzwerke. Grundlage dieser kumulativen Dissertation sind die Publikationen:

- *Keeser D, Padberg F, Reisinger E, Pogarell O, Kirsch V, Palm U, Karch S, Möller HJ, Nitsche MA, Mulert C. Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA) study.*

  Neuroimage. 2011 Mar 15;55(2):644-57.

- *Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, Brunelin J, Möller HJ, Reiser M, Padberg F. Prefrontal Transcranial Direct Current Stimulation Changes Connectivity of Resting-State Networks during fMRI.*

  Journal of Neuroscience. 2011 Oct 26;31(43):15284-93.

Beide Studien wurden doppelt-verblindet und plazebo-kontrolliert durchgeführt. In den Arbeiten wird mit zwei unterschiedlichen Verfahren, einem neurophysiologischen Ruhe- und einem aktiven Gedächtnistestparadigma (EEG), sowie mit einer funktionellen Konnektivitäts-Magnetresonanztomographie (fcMRT) nachgewiesen, dass präfrontale tDCS kortikale Netzwerke moduliert. Diese Ergebnisse sollen hier wiedergegeben und diskutiert werden. Die Verteilung, Ausrichtung und das Ausmaß der auf tDCS beruhenden Effekte auf die funktionelle Aktivität im Gehirn sind bisher wenig erforscht. Die Erarbeitung weiterer Hypothesen bezüglich der neurophysiologischen Wirkung von präfrontaler tDCS ist entscheidend, um Hinweise auf künftige experimentelle und therapeutische tDCS-Anwendungen zu erhalten.

Abstract

The principal purpose of the present thesis was to investigate the influence of prefrontal direct current stimulation (tDCS) on the modulation of cortical networks. The bases of this cumulative thesis are the two publications:

- *Keeser D, Padberg F, Reisinger E, Pogarell O, Kirsch V, Palm U, Karch S, Möller HJ, Nitsche MA, Mulert C. Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA) study.*

  Neuroimage. 2011 Mar 15;55(2):644-57.

- *Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, Brunelin J, Möller HJ, Reiser M, Padberg F. Prefrontal Transcranial Direct Current Stimulation Changes Connectivity of Resting-State Networks during fMRI.*

  Journal of Neuroscience. 2011 Oct 26;31(43):15284-93.

Both studies were carried out in a double-blinded, placebo-controlled manner. In the studies two different procedures, a neurophysiological electroencephalography (EEG) resting-state and an active EEG memory task paradigm, as well as a functional connectivity magnetic resonance imaging (fcMRI) procedure were used. Both studies proved that prefrontal tDCS modulates cortical networks.

These results are presented and discussed. The distribution, direction, and extent of tDCS mediated effects on brain physiology are not well understood. The development of further hypotheses with regard to the neurophysiological effects of prefrontal tDCS is crucial to obtain informations for future experimental and therapeutic tDCS applications.

Abkürzungsverzeichnis

%	Prozent
A/mm²	Ampere pro Quadratmillimeter
Abb.	Abbildung
cm²	Quadratzentimeter
CSD	Kortikal ausbreitende Depression (Cortical Spreading Depression)
DLPFC	Dorsolateraler präfrontaler Kortex
DMN	Default Mode Network
EEG	Elektroenzephalographie
fMRT	Funktionelle Magnetresonanztomographie
fcMRT	Funktionelle Konnektivitäts-Magnetresonanztomographie
fNIRS	Funktionelle Nahinfrarotspektroskopie
GABA	Gamma-Amino-Buttersäure Neurotransmitter
H15 2 O-PET	Positronenemissionstomographie mit O-15 Wasser
IFG	Inferiorer Frontaler Gyrus
M	Fingerbewegungen
M1	Motorkortex
µA	Mikroampere
mA	Milliampere
MEP	Motorisch Evoziertes Potential
mm²	Millimeter
MRS	Magnetresonanzspektroskopie
MRT	Magnetresonanztomographie
mV	Millivolt
PCC	Posteriorer cingulärer Kortex
R	Ruhe
rCBF	Regionaler zerebraler Blutfluß
SM	Somatomotorischer Kortex
SMA	Supplementär-Motorischer Kortex
SWS	Slow-Wave-Schlaf
tDCS	Transkranielle Gleichstromstimulation (transcranial Direct Current Stimulation)
TMS	Transkranielle Magnetstimulation

Abbildungsverzeichnis

Inhaltsverzeichnis

1 Einleitung

1.1 Die transkranielle Gleichstromstimulation (tDCS)

Die transkranielle Gleichstromstimulation ist ein neuromodulatorisches, nichtinvasives Gehirnstimulationsverfahren, das in ersten Studien die Kriterien für medizinische Sicherheit erfüllte (Nitsche et al., 2004; Iyer et al., 2005; Poreisz et al., 2007; Brunoni et al., 2011). Bei der tDCS wird ein kontinuierlicher Stromfluss, der nicht die Richtung ändert, durch an die Kopfhaut angelegte Schwammelektroden appliziert (siehe Abb. 1). Die zugrunde liegende Theorie des Wirkmechanismus basiert auf dem Nachweis, dass anodale tDCS zur Depolarisation einer großen Anzahl von Neuronen führt, während kathodale tDCS eine Hyperpolarisation von Neuronen hervorruft. Diese bipolare Stimulation führt zu Änderungen der kortikalen Erregbarkeit. Bei anodaler tDCS wurde eine exzitatorische Wirkung nachgewiesen, während kathodale tDCS inhibitatorisch wirkt (Nitsche et al., 2003c; Nitsche et al., 2003b; Nitsche et al., 2008). Vor 10 Jahren verschafften Nitsche und Paulus (Nitsche and Paulus, 2001) dieser schon länger bekannten Methode neue Popularität, als sie beim Menschen nachweisen konnten, dass anodale tDCS des Motorkortex die motorische Erregbarkeit erhöhte, während kathodale tDCS diese verminderte (Nitsche and Paulus, 2001; Nitsche et al., 2007). Die Stimulationswirkung ist abhängig von der Zeitdauer der Stimulation (siehe Abb. 2). Bereits kurze Stimulationslängen von ca. 10 Minuten erzeugen Post-Stimulationseffekte im menschlichen Motorkortex, die für bis zu einer Stunde und länger anhalten (Nitsche and Paulus, 2001; Nitsche et al., 2003a) .

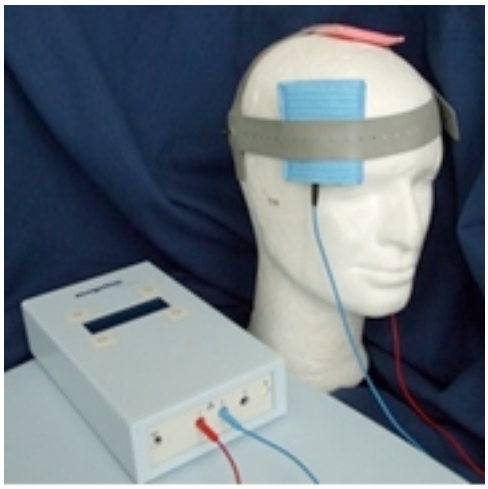

Abbildung 1
tDCS-Stimulator. Die Anode (+) ist über dem motorischen Kortex, die Kathode (-) über den supraorbitalen Kortex mittels Gummibändern befestigt.

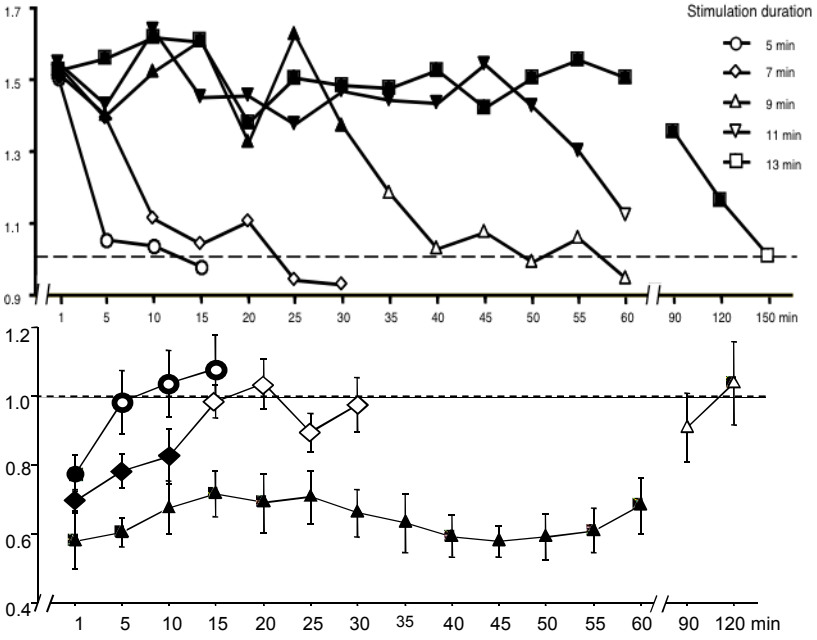

Abbildung 2:
Die Wirkung anodaler tDCS (obere Figur) und kathodaler tDCS (untere Figur) auf den Motorkortex. Die Erregbarkeit des Motorkortex wurde indirekt nachgewiesen durch die Bestimmung motorisch evozierter Potentiale (MEPs) und der Anwendung von transkranieller Magnetstimulation (TMS). Die gestrichelte Linie zeigt den Ausschlag der MEPs in Mikrovolt (y-Achse) während der Baseline-Bedingung. Abhängig von der Stimulationspolarität (obere Figur: anodale tDCS, untere Figur: kathodale tDCS) und dem Messzeitpunkt (x-Achse) lassen sich exzitatorische bzw. inhibitatorische Effekte bis zu 60 Minuten und darüber hinaus, abhängig von der Stimulationsdauer (5-13 Minuten), nachweisen.
(Abb. adaptiert von Nitsche et al. 2007)

Der primäre Wirkmechanismus scheint die Folge einer Schwellenmodulation des Ruhemembranpotentials zu sein (Pogosyan et al., 2009). Zudem spielt die Stromstärke eine wichtige Rolle. Bei der Verwendung von Schwammelektroden in der Größe von 25cm² und einer Stromintensität von 1mA ist eine kortikale Stromdichte der Intensität von 0,1 A/mm² anzunehmen (Miranda et al., 2006). Dies entspricht 10% des induzierten Stroms. Der Rest des Stroms wird durch die Haut, den Knochen und die Zerebrospinalflüssigkeit absorbiert (Wagner et al., 2007b)(siehe Abb. 3).

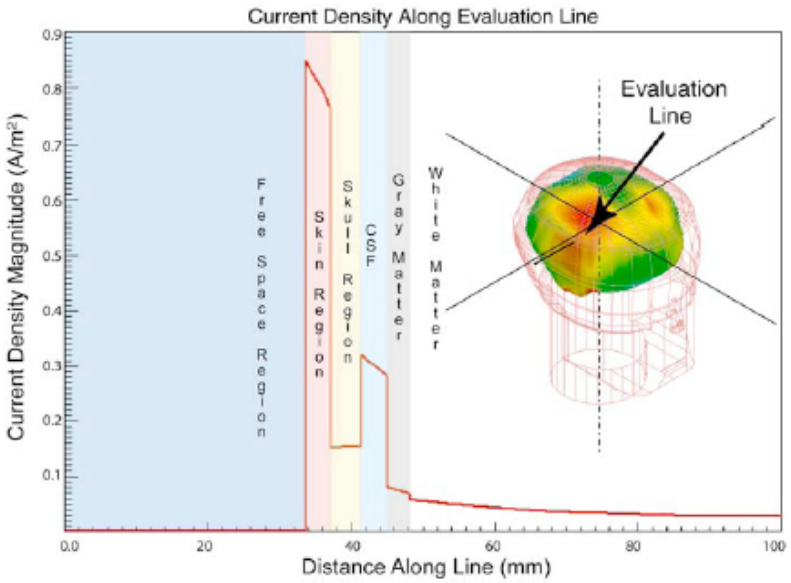

Abbildung 3:
Computerbasiertes Kopfmodell der tDCS nach Wagner und Kollegen.

(adaptiert von Wagner et al. 2007b)

Die transkranielle Gleichstromstimulation hat in den vergangenen 10 Jahren ein starkes Forschungsinteresse hervorgerufen (siehe Abb. 4). In diesem Zeitraum haben die Publikationen in internationalen Fachmagazinen rapide zugenommen (siehe Abb. 4) (Wagner et al., 2007a; Nitsche et al., 2008). Dabei ist der dorsolaterale präfrontale Kortex noch weniger gut untersucht worden als der Motorkortex.

Abbildung 4:
Anstieg von tDCS Publikationen in peer-reviewed Journals in den letzten 10 Jahren. Das Jahr 2011 ist bis einschließlich September berücksichtigt.

1.2 Präfrontale transkranielle Gleichstromstimulation

Die bisherigen Studien zur Stimulation des dorsolateralen Frontalhirns umfassen die Bereiche Sprache (Baker et al., 2010; Fertonani et al., 2010; Wirth et al., 2011), Gedächtnis (Elmer et al., 2009; Jo et al., 2009; Andrews et al., 2011; Hammer et al., 2011; Javadi et al., 2011; Javadi and Walsh, 2011; Marshall et al., 2011; Mulquiney et al., 2011; Teo et al., 2011), Exekutivfunktionen (Cerruti and Schlaug, 2009; Dockery et al., 2009), Depression (Fregni et al., 2006; Boggio et al., 2008b; Rigonatti et al., 2008; Ferrucci et al., 2009; Loo et al., 2010; Dell'osso et al., 2011; Martin et al., 2011; Palm et al., 2011), Schizophrenie (Vercammen et al., 2011), Tinnitus (Vanneste et al., 2010; Frank et al., 2011), Alzheimer (Boggio et al., 2009b), Schmerz (Boggio et al., 2008a; Arul-Anandam et al., 2009; Boggio et al., 2009a; Valle et al., 2009), soziale Interaktion (Knoch et al., 2008) und Risikoverhalten (Fecteau et al., 2007a; Fecteau et al., 2007b; Beeli et al., 2008a; Beeli et al., 2008b; Boggio et al., 2010b; Boggio et al., 2010a).

Aufgrund der überwiegend positiven Ergebnisse dieser Pilotstudien, die mit gesunden Probanden sowie mit psychiatrischen und neurologischen Patienten durchgeführt wurden, sind weitere Untersuchungen der präfrontalen tDCS als mögliche antidepressive Behandlungsform, als potentielle experimentelle und klinische Anwendung zur Beeinflussung der kognitiven Leistungsfähigkeit oder auch zur Modulation des Schmerzes vielversprechend. Insgesamt besteht allerdings noch großer Forschungsbedarf bezüglich der verwendeten Stimulationsprotokolle und der Wirkung auf klinische und neurobiologische/neurophysiologische Parameter. Die Anwendung von Elektroenzephalographie (EEG)-Untersuchungen zur Überprüfung möglicher tDCS-Stimulationseffekte könnte weiterführende Informationen über die neurophysiologischen Wirkmechanismen der tDCS liefern.

1.3 tDCS und Elektroenzephalographie (EEG)

Der Einfluss anodaler transkranieller Gleichstromstimulation auf das Ruhe-EEG wurde bereits von Pfurtscheller untersucht (Pfurtscheller, 1970). Pfurtscheller fand nach der anodalen Stimulation des Motorkortex mit 250 µA eine signifikante Abnahme der Theta (3-7 Hz)- und Alpha (8-12 Hz)-Aktivität. Eine kathodale Stimulation hingegen führte zu einer prozentualen Zunahme der Theta- und Alphaaktivität um ca. 10%.

Ardolino und Kollegen untersuchten den Effekt kathodaler Gleichstromstimulation (1,5 mA, 10 Minuten) auf die spontane neuronale Aktivität und die motorischen Reaktionen, die durch die Stimulation des zentralen und peripheren Nervensystems evoziert wurden (Ardolino et al., 2005). Von sechs gesunden Probanden (Alter 24-40 Jahre; Rechtshänder; Frauen und Männer) wurde das EEG vor und nach der tDCS-Stimulation aufgezeichnet. Die Kathode wurde über dem rechten motorischen Kortex platziert, die Anode oberhalb der Augenbrauen des linken Auges. Um mögliche unspezifische Effekte auszuschließen, erhielten weitere 5 Probanden eine Placebo-Stimulation. Vor der 15minütigen Stimulation des rechten motorischen Kortex wurde 6 Minuten lang die EEG-Aktivität in Ruhe aufgezeichnet, sowie nach der Stimulation erneut in 6 Minuten-Abschnitten (ebd.). In der rechten, kathodal stimulierten Gehirnhälfte zeigte sich ein signifikanter Effekt bei der totalen Power sowie bei der Delta- und Thetaaktivität, die sich jeweils erhöhten (ebd.). Die

Autoren folgern, dass kathodale Stimulation zur Erhöhung der langsamen EEG-Aktivität führt, was bereits von Creuzfeldt und Kollegen in frühen Arbeiten bei Katzen festgestellt werden konnte (Creutzfeldt et al., 1962). Die Placebostimulation zeigte statistisch keine Effekte, weder in der linken noch in der rechten Hemisphäre. Während des Slow-Wave-Schlafes (SWS) reduzierte bilaterale frontale sinusförmige anodale tDCS die durchschnittliche Power im Theta- und Alpha-1-Band in frontalen, zentralen und parietalen Elektroden-Lokalisationen (Marshall et al., 2004). Im Vergleich zur Placebo-Anwendung vergrößerte die frontale anodale tDCS während des SWS-reichen Schlafes das Erinnern, Wiederabrufen und Behalten von Wortpaaren, die nach dem Aufwachen abgefragt wurden. Weitere Studien mit transkraniellem Wechselstrom (transcranial alternating direct current) modulieren die EEG-Aktivität in Abhängigkeit von der gewählten Frequenz (Kanai et al., 2008; Kirov et al., 2009; Pogosyan et al., 2009; Zaehle et al., 2010; Feurra et al., 2011), wobei auch dem Vigilanzstatus eine Rolle zugeschrieben werden sollte (Marshall et al., 2011). Präfrontale tDCS (1mA, 15 Minuten, Anode dorsolateralpräfrontal, Kathode supraorbital und umgekehrt) während eines „n-back"- Gedächtnistests und gleichzeitiger EEG-Aufzeichnung modulierte die EEG-Aktivität in polaritätsspezifischer Hinsicht im niedrig-frequenten Theta- und Alphaband (Zaehle et al., 2011). Wir konnten reduzierte Delta und Theta (1-6,5 Hz) Aktivität und erhöhte Beta-1-Aktivität (13-18 Hz) im Ruhezustand nach präfrontaler tDCS (Anode F3, Kathode supraorbital, 2mA, 20 Minuten) feststellen, die sich quellenlokalisiert im Bereich des subgenualen Kortex zeigte (Keeser et al., 2011a). In einem anschließenden „n-back"- Gedächtnistest erhöhten sich P2- und P3-Potentiale verglichen mit der Placebo-Stimulation. Außerdem zeigte sich eine reduzierte Fehlerrate und eine Zunahme der Lösungsgenauigkeit speziell im höheren ‚memory-load' (2-back). Quellenlokalisiert konnte ebenfalls für den höheren ‚memory load' eine gestiegene EEG-Aktivität im linksseitigen parahippokampalen Gyrus festgestellt werden (Keeser et al., 2011a). Vanneste und Kollegen fanden nach präfrontaler tDCS mit entgegengesetzter Polarität (1,5 mA, 20 Minuten, Kathode F3, Anode supraorbital) bei Tinnitus-Patienten erhöhte Alpha-1-Aktivität (8-10 Hz) im subgenualen Kortex und reduzierte Beta- und Gamma-Aktivität (21,5-44 Hz) im rechten primären auditorischen Kortex (Vanneste and De Ridder, 2011). Jacobson und Kollegen stimulierten den rechten inferioren frontalen Gyrus (rIFG) mit der Anode und die linke supraorbitale Region mit der Kathode (Jacobson et al., 2011) über

eine Zeitdauer von 15 Minuten mit 1,5 mA Intensität. In ihrer Arbeit konnten sie eine Reduktion der Theta Power im rechten IFG feststellen, wo die Anode platziert wurde, während sich in der Region, wo die Kathode angelegt wurde, kein Stimulationseffekt zeigte (Jacobson et al., 2011). Vor kurzem veröffentlichten Wirth und Kollegen eine Untersuchung mit 20 gesunden Probanden, die anodal dorsolateral präfrontal links stimuliert wurden (1,5 mA, 7-37 Minuten), während die Kathode an der rechten Schulter angelegt wurde (Wirth et al., 2011). Im Vergleich zur Placebobehandlung reduzierte sich nach der Stimulation die Delta Power signifikant, während sich auf der Verhaltensebene die Sprachproduktion in Form einer Reduktion des semantischen Interferenzeffekts (einem Marker der bei Aphasiepatienten erhöht ist) veränderte. Die Modulation der EEG Aktivität kann auch in bildgebenden Verfahren visualisiert werden, was eine weitere Methode zum Wirknachweis der tDCS darstellt.

1.4 tDCS und bildgebende Verfahren

1.4.1 Motorkortex

Baudewig und Kollegen untersuchten den Einfluss der Gleichstromstimulation auf das fMRT- Signal. Bei sechs gesunden Probanden im Alter von 23-30 Jahren wurde der linke motorische Kortex für 5 Minuten mit 1mA stimuliert (Baudewig et al., 2001). Das fMRT BOLD-Signal wurde 5 und 15-20 Minuten nach der Stimulation gemessen. Fünf Minuten nach kathodaler Stimulation konnte eine signifikante Reduktion der Voxeldichte festgestellt werden ($p<0,01$), die auch noch 15-20 Minuten nach der Stimulation anhielt ($p<0,05$). Prozentual ausgedrückt, zeigte sich bei der ersten Messung eine Reduktion von 38% der Voxeldichte, bei der zweiten Messung eine Reduktion von 28%.

Metabolische Veränderungen durch die tDCS-Anwendung wurden auch in einer Studie von Lang und Kollegen nachgewiesen (Lang et al., 2005). Reale tDCS-Stimulation (anodal oder kathodal, 1mA, 10 Minuten) und Placebo-tDCS erfolgten an getrennten Tagen. Unmittelbar danach wurden sechs sequenzielle H15, 2 O-PET-Aufnahmen bei Ruhe (R) oder während Fingerbewegungen (M) aufgezeichnet. Die Reihenfolge der Intervention (wirkliches tDCS gegenüber Placebo-tDCS) und

die experimentellen Bedingungen (R gegenüber M) wurden über die Probanden hinweg randomisiert. Anodale tDCS erhöhte den regionalen zerebralen Blutfluss (rCBF) in vielen kortikalen und subkortikalen Gebieten im Vergleich zu kathodaler tDCS (siehe Abb. 5).

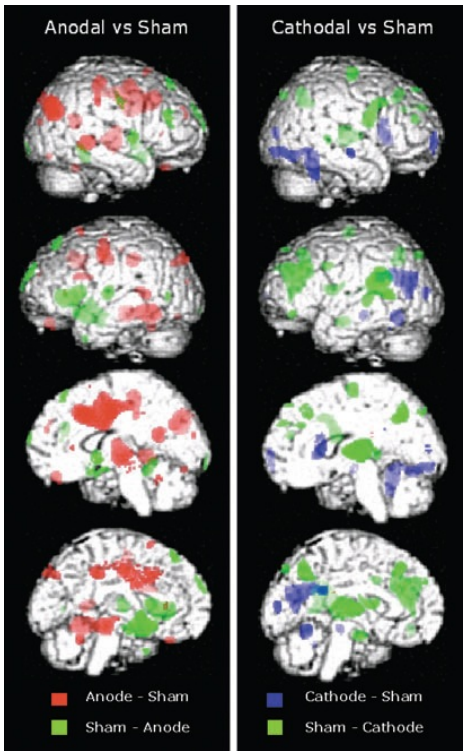

Abbildung 5:
Hauptwirkung anodaler und kathodaler tDCS im Vergleich zur Placebo Bedingung aufgezeichnet mit der Wasser-Positronen-Emissionstomographie ($H15\ 2\ O$-PET). Die farblichen Aktivierungen zeigen eine verhältnismäßige Zunahme oder Abnahme des regionalen zerebralen Blutflusses (rCBF) nach wirklicher tDCS-Stimulation gegenüber der Placebo-tDCS-Stimulation ($p < 0,05$). Die Bilder zeigen (von oben) die rechte laterale Oberfläche, die linke laterale Oberfläche, die rechte mittlere Oberfläche und die linke mittlere Oberfläche; (Abb. adaptiert von Lang et al., 2005).

Durch anodale Stimulation wurde die Aktivität im Stimulations-Gebiet erhöht (Gegend des motorischen Kortex M1 bestimmt durch transkranielle Magnetstimulation), während die kathodale Stimulation eine Erregungssabnahme der metabolischen Aktivität im korrespondierenden Gebiet zur Folge hatte. Jang und Kollegen stellten eine Zunahme der neuronalen Aktivierung im Motorkortex und damit verbundenen motorischen Arealen nach echter tDCS des linken Motorkortex (20 Minuten, Anode M1, Kathode supraorbital, 1mA) im Vergleich zu einer Scheinbehandlung durch erhöhte Blutoxygenierung im fMRT fest (Jang et al., 2009). Untersucht wurden jeweils 7 gesunde Probanden pro Stimulationsbedingung. In einer weiteren Bildgebungsstudie konnte gezeigt werden, dass anodale tDCS zu kurzlebigen Aktivierungszunahmen im linken primären Motorkortex (M1) und im supplementär-motorischen Kortex (SMA) in der Hemisphäre führte, die stimuliert wurde. Die Arbeitsgruppe um Johansen-Berg stimulierte 15 gesunde Probanden (Anode M1, Kathode supraorbital, 10 Minuten, 1mA)(Stagg et al., 2009a). Die Blutoxygenierung

nach der Stimulation verglichen mit Placebostimulation war höher als bei einer Scheinstimulation und der kathodalen tDCS, allerdings führte die kathodale tDCS zu einer Zunahme in der Aktivierung im kontralateralen M1 und im dorsalen prämotorischen Kortex (Stagg et al., 2009a). Zudem zeigte sich eine erhöhte funktionelle Konnektivität zwischen dem kontralateralen M1, dem prämotorischen M1 und dem direkt stimulierten M1 (ebd.). Um die netzwerkspezifischen Effekte des Motorkortexes nach tDCS-Stimulation bei 13 gesunden Probanden (Anode linker M1, Kathode supraorbital, 10 Minuten, 1mA) genauer zu erforschen, benutzten Polania und Kollegen (2011) eine funktionelle Ruhenetzwerk MRT Aufzeichnung, die sie mit einer voxelbasierten Graphenanalyse (zur Konzentration auf die hauptsächlichen funktionellen Verbindungen) auswerteten (Polania et al., 2011b). Sie fanden im Vergleich zur Placeboanwendung eine Abnahme in der durchschnittlichen Anzahl von direkten funktionellen Verbindungen vom linken somatomotorischen Kortex (SM) zu topologisch entfernten grauen Substanz-Regionen (ebd.). Darüber hinaus war eine Zunahme der funktionellen Konnektivität zwischen SM und dem linken prämotorischen, dem motorischen, und dem linken parietalen Kortex feststellbar. Diese Zunahme wurde begleitet von einer Erhöhung an funktioneller Konnektivität zwischen dem linken posterioren cingulären Kortex (PCC) und dem rechten dorsolateralen präfrontalen Kortex (DLPFC) (ebd.).

Antal und Kollegen fanden eine Reduktion der Blutoxygenierung in einer simultanen fMRT-tDCS Studie des linken motorischen Kortex (Anode M1, Kathode supraorbital, 10 Minuten, 1mA) bei 13 gesunden Probanden während eines gleichzeitig durchgeführten Finger-Tapping-Aufgabe (Antal et al., 2011). Die kathodale Stimulation hatte keine signifikante Wirkung, es zeigte sich aber eine Tendenz zur reduzierten Aktivierung (ebd.). In einer weiteren H_2O-PET Studie mit 9 gesunden Probanden konnten Paquette und Kollegen feststellen, dass die Interaktion von kathodaler tDCS-Stimulation des Motorkortex (Anode dominante Hemisphäre des Motorkortex, Kathode nicht-dominante Seite, 2mA, 4 Minuten pro Trial) und einer einfachen motorischen Aufgabe im Vergleich zur Placebo-Stimulation zu einer Reduktion des regionalen zerebralen Blutflusses unterhalb der Kathode führte (Paquette et al., 2011). Die Autoren diskutieren, ob es die Interaktion zwischen Aufgabe und Stimulation ist, die zu regionalen zerebralen Blutfluss (rCBF)-Veränderungen führt (ebd.). Polonia und Kollegen führten eine weitere maskenbasierte funktionelle MRT-Konnektivitätsstudie an 13 gesunden Probanden durch,

indem sie den Motorkortex mit einer Scheinstimulation, einer anodalen tDCS oder einer kathodalen tDCS stimulierten (Anode M1, Kathode supraorbital, 10 Minuten, 1mA) (Polania et al., 2011a). Sowohl die funktionelle Konnektivität zwischen dem Thalamus und dem ipsilateralen M1, als auch die funktionelle Konnektivität zwischen dem linken Nucleus Caudatum und dem parietalen Kortex waren signifikant erhöht im Vergleich von echter zur Scheinstimulation. Kathodale tDCS über M1 reduziert hingegen die funktionelle Koppelung zwischen dem linken M1 und dem kontralateralen Putamen (ebd.).

Stagg und Kollegen untersuchten die Neurotransmitterkonzentration mit Magnetresonanzspektroskopie (MRS) nach anodaler, kathodaler oder einer Schein-tDCS des Motorkortex (Anode M1, Kathode supraorbital rechts, 1mA, 10 Minuten) und konnten eine Reduktion der inhibitorischen Gamma-Amino-Buttersäure (GABA)-Neurotransmitterkonzentration feststellen, während kathodale tDCS Glutamat und ebenfalls GABA reduzierte (Stagg et al., 2009b). In einer weiteren Arbeit fanden Stagg und Kollegen, dass die Reduktion an GABA-Konzentration nach anodaler M1-Stimulation verglichen mit einer Scheinbehandlung positiv mit dem Grad motorischen Lernens und der Veränderung des fMRT Signals korrelierte (Stagg et al., 2011). Bisher gibt es noch wenige bildgebende Studien hinsichtlich der Stimulation des präfrontalen Kortex.

1.4.2 Präfrontale tDCS

Merzagora und Kollegen verwendeten funktionelle Nahinfrarotspektroskopie (fNIRS) (Merzagora et al., 2009), um die Effekte der bilateralen präfrontalen tDCS zu untersuchen (Anode Fp1, Kathode Fp2, 10 Minuten, 1mA). Sie beobachteten in der Nähe der Anode eine lokale relative Zunahme der Konzentration von Oxyhämoglobin.

In der von uns durchgeführten funktionellen MRT-Konnektivitätsstudie konnten wir erhöhte funktionelle Konnektivität bei 13 gesunden Probanden im sogenannten ‚Default Mode Netzwerk' und im ‚fronto-parietalen Netzwerk' nach präfrontaler tDCS im Vergleich zu einer Scheinstimulation (Anode linker dorsolateraler präfrontaler Kortex, Kathode supraorbital rechts, 20 Minuten, 2mA) feststellen (Keeser et al., 2011b). Pena-Gomez und Kollegen fanden ebenfalls nach präfrontaler Gleichstromstimulation (Anode/Kathode dorsolateral-präfrontal links, Katho-

de/Anode supraorbital rechts, 2mA, 20 Minuten) erhöhte fronto-parietale funktionelle Konnektivität, während sich das DMN deaktivierte (Pena-Gomez et al., 2011). Die Wirkung von tDCS am Menschen konnte mit Hilfe von bildgebenden Verfahren in ersten Studien nachgewiesen werden. Am Tier- und Computermodell gibt es weitere modellierte neurophysiologische Arbeiten, die zusätzliche wertvolle Informationen liefern.

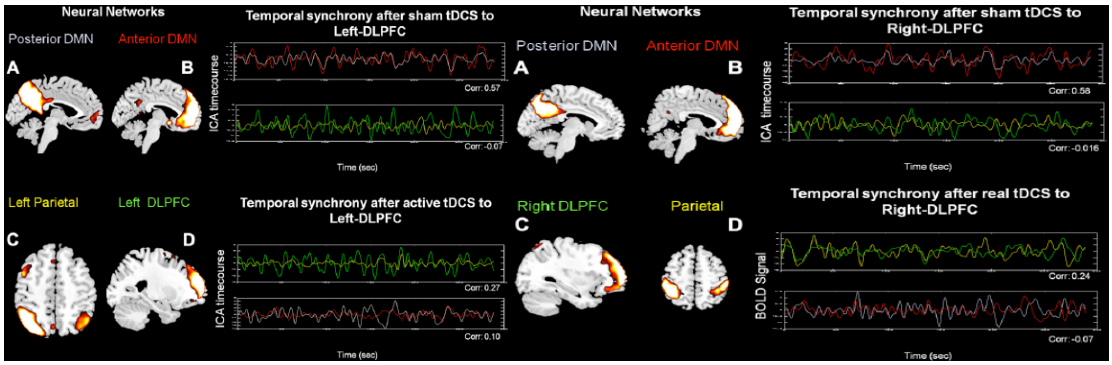

Abbildung 6:
Modulation der frontalen-parietalen Konnektivität (C, D) nach echter präfrontaler tDCS, während das sogenannte Default-Mode-Netzwerk (DMN) unter der Scheinstimulation (A,B) unverändert geblieben ist (Anti-Korrelation nach echter präfrontaler tDCS). Bild links: Anode links DLPFC, Kathode supraorbital-rechts, Bild rechts: Anode rechts DLPFC, Anode supraorbital-links.
(Abb. adaptiert von Pena-Gomez et al. 2011)

1.5 Tierexperimentelle Untersuchungen und computerbasierte Modelle

In tierexperimentellen Untersuchungen wurde bereits Anfang der 60er Jahre entdeckt, dass anodale Gleichstromstimulation von mehr als 5 Minuten zu einer unterschwellige Depolarisierung des Ruhemembranpotentials führte, was zu einem Anstieg der neuronalen Spontanaktivität führte, während kathodale Gleichstromstimulation eine Hyperpolarisierung des Ruhemembranpotentials mit einem Abfall neuronaler Spontanaktivität erzeugte (Creutzfeldt and Struck, 1962; Bindman et al., 1964; Purpura and McMurtry, 1965), siehe Abb. 7.

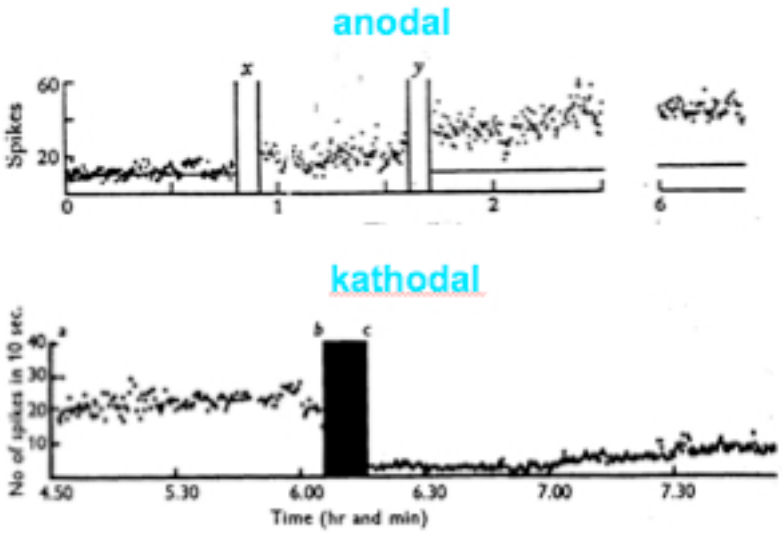

Abbildung 7:
Bindmann und Kollegen (1964) stimulierten den primären sensorischen Kortex von Ratten. Die Aktionspotentiale der stimulierten Rattenkortexe wurden kontinuierlich aufgezeichnet (Baseline-Aktivität zu Beginn). Die weißen Balken (x, y) zeigen die anodale Stimulation für 20 Minuten mit einer Intensität von 0.25 µA, während der schwarze Balken (b, c) den Beginn der kathodalen Stimulation angibt. Anhand der x-Achse (Zeit in Stunden) sieht man eine Zunahme der Aktionspotentiale nach anodaler Stimulation (obere Grafik), während kathodale Stimulation zu einer Abnahme der neuronalen Aktivität führte (Grafik unten). Die Stimulationen zeigten Nacheffekte, die bis zu mehreren Stunden nachweisbar waren. (Abb. adaptiert von Bindman et al. 1964)

Die anodale tDCS des sensomotorischen Kortex mit einer Stimulationsintensität von 3 mA für 30 Minuten bei Ratten erhöhte die Kalziumionen über das Stimulationsende hinaus (Islam et al., 1995). Die Erhöhung war sowohl in der stimulierten Hemisphäre als auch im Hippocampus und im Thalamus bis 24 Stunden nach der Stimulation feststellbar (ebd.).

Weitere elektrophysiologische Untersuchungen von Bikson und Kollegen zeigten, dass die Gleichstromstimulation von Ratten-Hippocampus-Schnitten die Netzwerkfunktion, sowie die Exzitabilität kurz- und langfristig veränderte (Bikson et al., 2004). Die maximale Stimulation zeigte sich in den basalen und apikalen Dentriten (ebd.).

An Ratten wurde zudem die kortikal sich ausbreitende Depression (CSD) untersucht, wobei nur die anodale tDCS einen signifikanten Effekt auf die CSD ausübte, was als ein Indikator für den Grad der kortikalen Erregbarkeit angesehen werden kann (Liebetanz et al., 2006a). Zudem wurde in Ratten der antikonvulsive Effekt bei Epilepsie untersucht und diskutiert (Liebetanz et al., 2006b). Anhand von Ratten-Hippocampus-Schnittexperimenten und einer computerunterstützten Modellierung konnten Reato und Kollegen nachweisen, dass schwacher Gleichstrom die neuronale Feuerungsrate in einer asymmetrischen, aber ausgeglichenen Weise moduliert (Reato et al., 2010). Eine weitere Arbeit von Wachter und Kollegen brachte den Nachweis, dass tDCS die kortikale Blutperfusion in einer polaritätsspezifischen Weise verändert, wo anodale tDCS von 0,1 mA den zerebralen Blut-

fluss um 25% erhöhte, während kathodale tDCS den umgekehrten Effekt zur Folge hatte (Wachter et al., 2011). Erhöhte fMRT Signalintensitäten konnten in der Ratte im frontalen Kortex und im Nucleus Accumbens nach anodaler tDCS festgestellt werden, was ein Hinweis dafür ist, dass frontale tDCS neuronale Aktivierung im frontalen Kortex und verbundenen Arealen zur Folge hat (Takano et al., 2011). In einer ersten Pilotstudie wurde die Rolle des kortikalen Zelltyps hinsichtlich des elektrisch induzierten Feldes in Motorkortex-Schnitten von Ratten untersucht (Pogosyan et al., 2009). Das Soma der Pyramidalneurone aus der Schicht 5 zeigte sich am sensitivsten gegenüber der Polarisation (ebd.). Ferner betonen die Autoren, dass basale wie auch apikale Dendriten in entgegengesetzte Richtungen polarisiert werden (siehe Abb. 8), so dass man nicht davon ausgehen kann, dass ein elektrisches Feld eine global polarisierende oder depolarisierende Wirkung ausübt (ebd.).

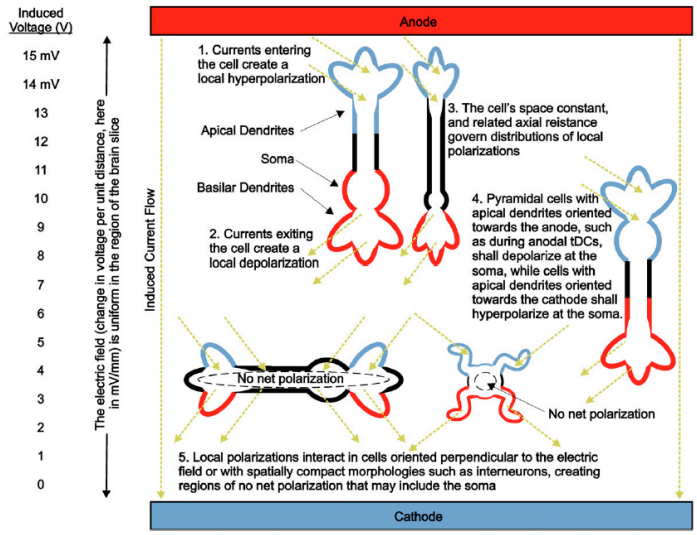

Abbildung 8:
Schematisch dargestelltes Modell der kortikalen Neuronen-Polarisation durch Gleichstromstimulation. Ein konstanter Gleichstrom wird zwischen den Stimulationselektroden (rot:Anode, blau:Kathode) appliziert. Die induzierten elektrischen Ströme über einen gleichartigen spezifischen Widerstand, schaffen einen gleichförmigen Stromspannungsanstieg zwischen der Anode und der Kathode. Da das elektrische Feld gleichförmig ist, hat die absolute Position eines Neurons zwischen der Anode und der Kathode keine Bedeutung. (1,2) blaue Membran: induzierte Hyperpolarisation; rote Membran: induzierte Depolarisation. (3) Die Zellmembranenbiophysik und die Zellmorphologie bestimmen die Polarisation hinsichtlich des elektrischen Felds. (4) Position des Soma im Dendriten-Baum bestimmt, ob es depolarisiert oder hyperpolarisiert wird. (5) Bestimmte Morphologien der Zelle können dazu führen, dass diese nicht polarisiert werden, auch wenn die Dendriten polarisiert werden.

(Abb. adaptiert von Radman et al. 2009)

Um die Verteilung des durch tDCS induzierten elektrischen Feldes im Gehirn vorherzusagen, wurden verschiedene Elektroden-Positionen mathematisch modelliert (Miranda et al., 2006; Wagner et al., 2007b). Ein kugelförmiges Standardkopfmodell unter verschiedenen bipolaren Elektrodenmontagen und einer Stimulationsintensität von 2 mA führte zu kortikalen Stromdichten von 0.01 mA/cm2 (Miranda et al., 2006), während Wagner und Kollegen (Wagner et al., 2007b) Stromdichtemaxima zwischen 0.77 und 2 mA/cm2 für unterschiedliche Elektroden-Montagen nach der theoretischen Induktion von 1 mA tDCS in einem

realistischen MRI-basierten Finite-Elemente-Kopfmodell errechneten. Die bisherige Modellierung zeigte eine beachtenswerte Induktion von Stromdichten nach tDCS-Applikation. Miranda und Kollegen, als auch Wagner und Kollegen konnten ferner ein nicht-fokales elektrisches Feld nahe der Stimulationselektroden nachweisen (Miranda et al., 2006; Wagner et al., 2007b). Eine weitere Modellstudie, die das anisotrope Gewebe der weißen Substanz in ihrer Studie besonders berücksichtigte, kam zu dem Ergebnis, dass die weiße Substanz einen signifikanten Effekt auf die Stimulation des Gehirns habe (Suh et al., 2009). Zudem benötige man nur 0,5 mA direkt unter der Anode, um eine Stromstärke von 0,31mV/mm zu erzeugen, während es 2,02 mA in einem fixen isotropischen Modell gewesen sind und 2,39 mA und 2,39 mA in einem variablen anisotropischen Modell (ebd.). Die optimale Stimulationskonfiguration wird auch in einer Studie an Schmerzpatienten diskutiert, in der wiederum anhand eines Finite-Elemente-Kopfmodells und klinischen Ergebnissen die supraorbitale Elektrode effektiv gewesen ist. Die anodale und die kathodale Stimulation führten zu ähnlichen Ergebnissen. Das Resultat hatte für eine Elektrode außerhalb des Kopfbereichs (extracephalic electrode) für den Bereich Schmerz allerdings klinisch keinen Effekt (Mendonca et al., 2011).

2 Orginalarbeiten und Manuskripte

■ **Keeser D, Padberg F, Reisinger E, Pogarell O, Kirch V, Palm U, Karch S, Möller HJ, Nitsche MA, Mulert C** (2011). Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: A standardized low resolution tomography (sLORETA) study. *NeuroImage* 55(2): 644-657.

■ **Keeser, D, Bor, J, Meindl, T, Reiser, M, Palm, U, Pogarell, O, Mulert, C, Padberg, F.** Prefrontal transcranial Direct Current Stimulation (tDCS) mudulates resting-state functional connectivity in healthy subjects: a functional magnetic resonance imaging (fMRI) study. *Journal of Neuroscience* 31(43):15284-93.

2.1 Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: A standardized low resolution tomography (sLORETA) study

Bis zu dem Zeitpunkt unserer Veröffentlichung hat es keine EEG-Untersuchung mit präfrontaler tDCS im wachen Ruhezustand und während einer Arbeitsgedächtnisaufgabe gegeben. Wir untersuchten den Zusammenhang zwischen präfrontaler Gleichstromstimulation (Anode dorsolateral-präfrontal links, Kathode rechts-supraorbital, 2 mA, 20 Minuten) und der EEG-Aktivität im Ruhezustand und während eines Arbeitsgedächtnistests („n-back"-Test). Verglichen mit einer Placebostimulation führte die echte Gleichstromstimulation zu einer Modulation von Deltaaktivität im Ruhezustand. Als mögliche Quelle für die EEG-Oberflächenveränderungen zeigte sich reduzierte Delta-Theta Power im Bereich des subgenualen Kortex (BA 25) und des anterioren Cingulums (BA 32). In dem anschließenden „n-back"-Test erhöhte die echte tDCS die Gedächtnisleistungen (Fehlerrate, Genauigkeit, Reaktionszeit). Dies ging einher mit erhöhten P2- und P3-Amplituden der ereigniskorrelierten Potentiale für die 2-back Kondition. Quellenlokalisiert konnte erhöhte Aktivität im ‚parahippokampalen Gyrus' links festgestellt werden. Diese Ergebnisse unterstützen die Hinweise, dass präfrontale tDCS neuronale Aktivität moduliert und die Gedächtnisleistungen verbessert.

NeuroImage 55 (2011) 644–657

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: A standardized low resolution tomography (sLORETA) study

D. Keeser [a,1], F. Padberg [a,*,1], E. Reisinger [a], O. Pogarell [a], V. Kirsch [a], U. Palm [a], S. Karch [a], H.-J. Möller [a], M.A. Nitsche [b], C. Mulert [a,c]

[a] Department of Psychiatry and Psychotherapy, Ludwig-Maximilian University Munich, Germany
[b] Department of Clinical Neurophysiology, Georg-August University, Goettingen, Germany
[c] University Medical Center Hamburg-Eppendorf, Department of Psychiatry and Psychotherapy, Psychiatry Neuroimaging Branch (PNB), Hamburg, Germany

ARTICLE INFO

Article history:
Received 30 July 2010
Revised 3 November 2010
Accepted 2 December 2010
Available online 10 December 2010

Keywords:
Transcranial direct current stimulation (tDCS)
sLORETA
Major depression
Therapy
Cognition
Prefrontal

ABSTRACT

Prefrontal transcranial direct current stimulation (tDCS) with the anode placed on the left dorsolateral prefrontal cortex (DLPFC) has been reported to enhance working memory in healthy subjects and to improve mood in major depression. However, its putative antidepressant, cognitive and behavior action is not well understood. Here, we evaluated the distribution of neuronal electrical activity changes after anodal tDCS of the left DLPFC and cathodal tDCS of the right supraorbital region using spectral power analysis and standardized low resolution tomography (sLORETA). Ten healthy subjects underwent real and sham tDCS on separate days in a double-blind, placebo-controlled cross-over trial. Anodal tDCS was applied for 20 min at 2 mA intensity over the left DLPFC, while the cathode was positioned over the contralateral supraorbital region. After tDCS, EEG was recorded during an eyes-closed resting state followed by a working memory (n-back) task. Statistical non-parametric mapping showed reduced left frontal delta activity in the real tDCS condition. Specifically, a significant reduction of mean current densities (sLORETA) for the delta band was detected in the left subgenual PFC, the anterior cingulate and in the left medial frontal gyrus. Moreover, the effect was strongest for the first 5 min ($p<0.01$). The following n-back task revealed a positive impact of prefrontal tDCS on error rate, accuracy and reaction time. This was accompanied by increased P2- and P3- event-related potentials (ERP) component-amplitudes for the 2-back condition at the electrode Fz. A source localization using sLORETA for the time window 250–450 ms showed enhanced activity in the left parahippocampal gyrus for the 2-back condition. These results suggest that anodal tDCS of the left DLPFC and/or cathodal tDCS of the contralateral supraorbital region may modulate regional electrical activity in the prefrontal and anterior cingulate cortex in addition to improving working memory performance.

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that shifts neuronal resting membrane potentials towards depolarization or hyperpolarization, depending on whether anodal or cathodal stimulation is applied, leading to changes of cortical excitability and other functional parameters (Nitsche et al., 2008, 2003a,b). More recently, Nitsche and Paulus (2000, 2001) revisited this approach in humans and demonstrated that anodal tDCS increases and cathodal tDCS decreases motor cortex excitability (Nitsche and Paulus, 2000, 2001). When applied for 9–13 min, tDCS produces post-stimulation effects in the human motor cortex that are stable for up to 1 h and longer (Nitsche et al., 2003c; Nitsche and Paulus, 2001). As demonstrated in animal experiments, the primary mechanism of tDCS appears to be a subthreshold modulation of neuronal resting membrane potential (Purpura and McMurtry, 1965). Accordingly, pharmacologically blocking voltage-dependent ion channels in humans abolishes any effect of depolarizing anodal tDCS on cortical excitability, but does not influence the impact of hyperpolarizing cathodal tDCS (Nitsche et al., 2003a). Pharmacological studies have proven that tDCS related effects depend on changes of NMDA receptor-efficacy (Liebetanz et al., 2002). Recently, Stagg et al. (2009) demonstrated changes in GABA levels after anodal tDCS using magnetic resonance spectroscopy (MRS), suggesting that anodal excitatory effects do affect GABAergic inhibition in addition to NMDA-receptor dependency (Stagg et al., 2009). Based on initial studies, combining tDCS and EEG, a direct impact of tDCS on oscillatory activity was observed (Ardolino et al., 2005; Marshall et al., 2004). During slow-wave sleep (SWS) bilateral frontal

* Corresponding author. Department of Psychiatry and Psychotherapy, Ludwig-Maximilians University Munich, Nussbaumstrasse 7, D-80336 Munich, Germany. Fax: +49 89 51603930.
E-mail address: padberg@med.uni-muenchen.de (F. Padberg).
[1] Both authors contributed equally to the manuscript.

1053-8119/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2010.12.004

sinusoidal anodal tDCS reduced the average power in the theta and alpha-1-bands in frontal, central and parietal electrode locations (Marshall et al., 2004). Compared to placebo stimulation, frontal anodal tDCS during SWS-rich sleep distinctly increased the retention of word pairs (Marshall et al., 2004). Ardolino et al. (2005) also found a widespread impact of tDCS on the EEG (Ardolino et al., 2005). Increasing amounts of delta and theta activity were found after cathodal DC stimulation (15 min, 1.5 mA) to the right motor cortex, extending beyond the primary stimulation site (Ardolino et al., 2005). These EEG pilot studies are indicative of possible large-scale network changes following tDCS. Using positron emission tomography, Lang et al. (2005) showed that anodal tDCS increased the rCBF in widespread cortical and subcortical areas in comparison to cathodal tDCS, while cathodal stimulation entailed an excitability decrease of the metabolic activity in the corresponding areas (Lang et al., 2005).

One mode of tDCS application, namely anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC) and cathodal stimulation of the right supraorbital region, has been associated with working memory enhancement and improvement in other cognitive domains (Boggio et al., 2006; Dockery et al., 2009; Elmer et al., 2009; Ferrucci et al., 2008; Fertonani et al., 2010; Fiori et al., 2010; Fregni et al., 2005; Kincses et al., 2004; Marshall et al., 2004; Ohn et al., 2008).

Memory processes of healthy subjects were enhanced after left anodal DLPFC tDCS with the cathode placed on the right frontocortical regions (Fregni et al., 2005; Kincses et al., 2004; Marshall et al., 2004, 2005; Ohn et al., 2008). Moreover, prefrontal tDCS is supposed to modulate pain perception (Boggio et al., 2009, 2008b), seems to influence social behavior (Knoch et al., 2008) and shows an impact on risk taking behavior (Beeli et al., 2008a,b; Fecteau et al., 2007a,b). Prefrontal tDCS may even influence the desire for specific foods (Fregni et al., 2008) and the reaction time to lies (Priori et al., 2008).

In depressed subjects promising pilot data of prefrontal tDCS were reported, suggesting a therapeutic action of real tDCS compared to sham tDCS (Boggio et al., 2007, 2008a; Ferrucci et al., 2009; Fregni et al., 2006; Rigonatti et al., 2008), whereas the effect of one single tDCS-session on healthy subjects had no mood-altering effects (Koenigs et al., 2009).

The mechanism of action of prefrontal tDCS is not completely understood and to date there has been no study about the effects of prefrontal tDCS on resting EEG. Moreover, as prefrontal tDCS seems to influence a wide range of disorders and behaviors, resting state EEG and source analysis techniques may help to better understand prefrontal tDCS induced post-stimulation effects. Furthermore, TMS, MRS and imaging studies are only an indirect proof of the neuronal activity and were predominantly applied to the motor cortex in the past to test the effects of tDCS on brain physiology. We therefore investigated the effects of anodal tDCS of the left DLPFC and cathodal tDCS of the supraorbital region in a placebo-controlled cross-over study in healthy subjects, applying resting state EEG with spectral power analysis and standardized low resolution tomography (sLORETA). Following resting-state EEG all healthy subjects underwent a working memory task (n-back) with event-related potential (ERP) recording. As prefrontal tDCS has been found to influence working memory performance, we intended to replicate this behavioral finding and hypothesized that neurophysiological correlates should be detectable in ERPs related to cognitive processes.

Methods and materials

Subjects

Ten healthy subjects (five women, five men, mean age = 28.89 years, SD = 2.67) participated in this study. All subjects underwent a semi-

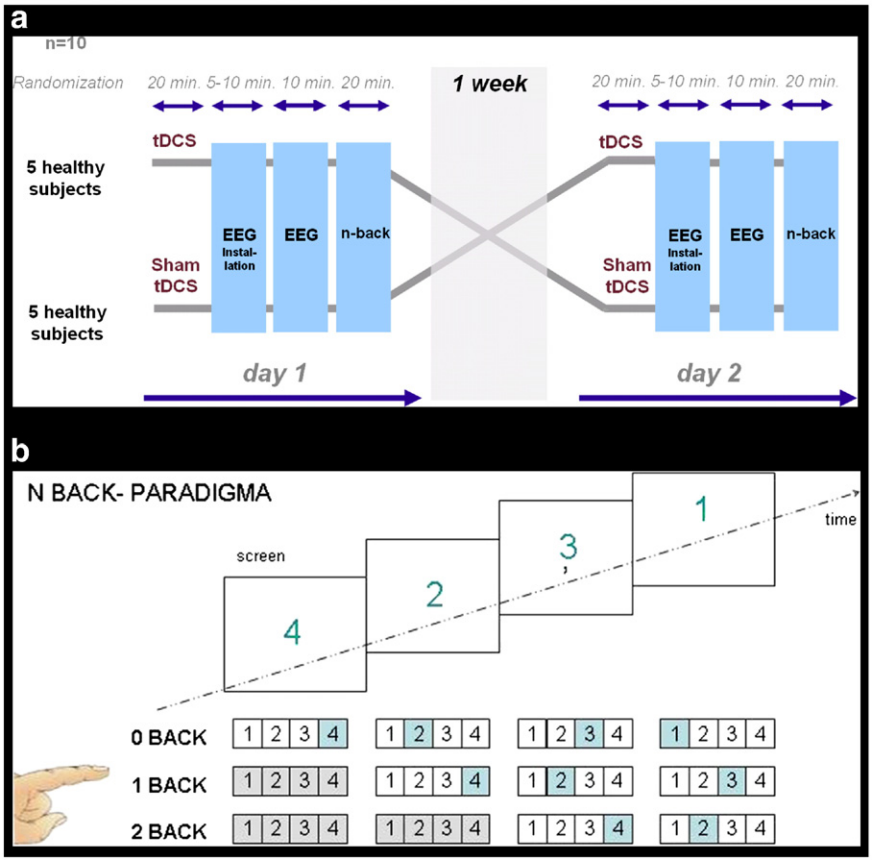

Fig. 1. a) experimental design (prior to the experiments the healthy subjects were introduced and trained to the n-back-task). b) n-back working memory paradigm.

structured interview (including the M-CIDI-S interview and a semantic word fluency task (Wittchen and Müller, 1998) showing that they were without history of neurological and/or psychiatric diseases and free of medication affecting the central nervous system. All subjects were right-handed (Edinburgh handedness test (Oldfield, 1971)) and homogenous with regard to education (university masters degree or medical students). This study was approved by the local ethics committee of the Faculty of Medicine, Ludwig-Maximilian University Munich, Germany. Written informed consent was obtained from each subject and they were paid for their participation. All subjects underwent single sessions of active anodal tDCS and sham tDCS on separate days in randomized order with both conditions counterbalanced across subjects and with an intersession interval of at least 1 week (see Fig. 1a). In addition, mood changes were assessed using the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988) before and after tDCS and after the end of EEG recording.

tDCS

An Eldith DC stimulator approved for use in humans was used for active stimulation (Neuroconn, Ilmenau, Germany). For sham tDCS, a custom-built placebo stimulator (Neuroconn, Ilmenau, Germany) was used, which was indistinguishable from the active tDCS device to both the operator who administered tDCS and the subjects participating in the trial. Two water-soaked sponge electrodes were used for stimulation (7×5 cm, 35 cm^2). The anode was placed above the left DLPFC with the center above F3 (10–20 system) and the cathode above the right supraorbital region, as previously reported (Fregni et al., 2006). Each tDCS condition was applied for 20 min (15 s ramp in and 15 s ramp out) at 2 mA stimulation intensity. The impedance was controlled by the device, normally ranging below 10 kΩ, limited by the voltage at less than 26 V.

EEG recording

Acute effects of tDCS on the EEG were assessed using a Neuroscan Synamps apparatus together with an electrode cap with 32 electrodes. The recordings took place approximately 5–10 min after each tDCS treatment session with 25 electrodes (all referred to channel Cz). Electrode skin impedance was always less than 5 kΩ. The electrodes were placed according to the International 10/20 system (Jaspers, 1958) with the additional electrodes FC1, FC2, FC5, FC6, CP5 and CP6. The electrooculogram was measured below the left eye and Fpz served as ground electrode. The subjects were instructed to remain in an alert state with their eyes closed in a sound-attenuated room. The EEG was recorded for 10 min with a sampling rate of 1000 Hz and an analogous bandpass filter (0.16–200 Hz). Offline, we changed the sampling rate to 250 Hz and used a 70 Hz low-pass filter. Before analysis, artifact detection was performed automatically (threshold 70 microvolt (μV)) and visually involving all EEG channels and EOG with the exclusion of all EEG segments that contained obvious eye or muscle artifacts or a decrease in alertness. Additionally, the EEG was analyzed four times independently by two experienced neurophysiologists blinded to the stimulation condition. After relation to the average reference, spectral analysis was performed for 25 electrodes (due to electrode and/or muscle artifacts in some subjects, it was necessary to exclude the electrodes T1, T2, P09 and P10 in the whole sample). The EEG was Fourier-transformed for at least 2-second epochs using the Brain Vision Analyzer software Version 1.05. Epochs were reduced to an average of 160 artifact-free epochs (2 min and 40 s) for the entire sample. The EEG epochs were acquired choosing the best quality, excluding blinking, muscle and electrode artifacts. At least 100 artifact-free segments were required from each subject for fast Fourier transformation and power spectral analysis (PSD) of the Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–25 Hz) and Gamma (30–40 Hz) frequency bands. Repeated-measure analyses of variance (ANOVAs) were used to test for differences between the conditions (anodal vs. sham) in EEG absolute power (μV^2). Multivariate normal distribution was checked with the Mauchly test of sphericity, and the Greenhouse-Geisser correction was applied, when necessary. A p value <0.05 was considered significant. Student's t-tests were used for post hoc analysis (single electrode comparisons). Statistics were performed using the SPSS 13.0 software (Statistical Package for Social Sciences, SPSS Inc, Chicago).

sLORETA

We performed a current density analysis in 3-D Tailarach/MNI space of the scalp-recorded electrical activity using the sLORETA/eLORETA software package (Pascual-Marqui, 2002). LORETA images represent the electrical activity of each voxel in the neuroanatomic Talairach/MNI space as amplitude of the computed current source density ($\mu A/mm^2$). LORETA estimates the distribution of electrical neural activity in the 3-D space, based on the measurements of a dense grid of electrodes, which are placed on the entire scalp surface covering the brain. The first version of LORETA (Pascual-Marqui et al., 1994) has been validated extensively in the past using PET (Pae et al., 2003; Pizzagalli et al., 2004; Zumsteg et al., 2005b), functional magnetic resonance imaging fMRI (Mulert et al., 2004; Vitacco et al., 2002) and intra-cerebral recordings (Zumsteg et al., 2005a, 2006). Moreover, even deep structures with mesial hippocampal and subcallosal cingulate foci could be correctly classified with LORETA in the past (Pizzagalli et al., 2004; Zumsteg et al., 2005b). Pizzagalli et al. (2004) demonstrated a highly correlated correspondence between LORETA measures of activation in subgenual cingulate and PET measures of glucose metabolism (Pizzagalli et al., 2004). These results can also be applied on sLORETA (Pascual-Marqui, 2002), which is an advanced version of the previous LORETA method.

The version of LORETA used in the present study, sLORETA (Pascual-Marqui, 2002), estimates the current source density distribution for epochs of brain electrical activity on a dense grid of 6239 voxels at 5 mm spatial resolution. The effects of tDCS on sLORETA were obtained for both experimental conditions (real and sham tDCS) and compared between groups with t-statistical non-parametric mapping, using the implemented statistical nonparametric mapping (SnPM) tool. The significance level applied to the data was set at $p<0.05$ (significant effect) and $p<0.10$ (statistical trend).

n-back task

Prior to tDCS experiments (study design, see Fig. 1a) a baseline n-back task was conducted on a separate day. Following EEG recordings after real or sham tDCS, all subjects underwent the same working memory n-back task (see Figs. 1a,b). In the n-back paradigm figures of cardinal numbers 1–4 were presented in pseudorandomized order on the screen with an interval of 1800 ms between stimuli. Each number was presented for 400 ms. The easiest task consisted of simply pressing the key that appeared immediately on the screen (0-back). For 1-back the number which was presented a passageway before had to be pressed. 2-back required to press the

Table 1
PANAS mean ratings and standard deviations before and after real or sham stimulation.

	Real tDCS and EEG		Sham tDCS and EEG	
	Before	After	Before	After
PANAS				
Positive affect	26.80 (5.14)	27.60 (5.69)	28.00 (5.14)	27.10 (3.84)
Negative affect	11.40 (2.55)	11.50 (2.17)	11.60 (2.01)	11.10 (1.91)

button according to the number presented two trials back. The different conditions were presented in 6 blocks and every block consisted of 14 trials. The subjects were informed about all tasks at the beginning by displaying 0-, 1-, and 2-back on the center of the screen between blocks and as headline during the whole experiment. Stimulus presentation was computerized (Presentation, Version 9.13). In order to ensure that participants can principally perform the task, they could practice several minutes before the recording started.

ERP recording

Eye artifact correction

Eye artifact and brain activities were considered as concurrent overlapping processes and separated using the principle of multiple source artifact correction in BESA 5.1.4.40 software (MEGIS, Graefelfing, Germany): Therefore first a provided surrogate model (BR_Brain Regions.LR.bsa) consisting of a set of dipole sources was placed

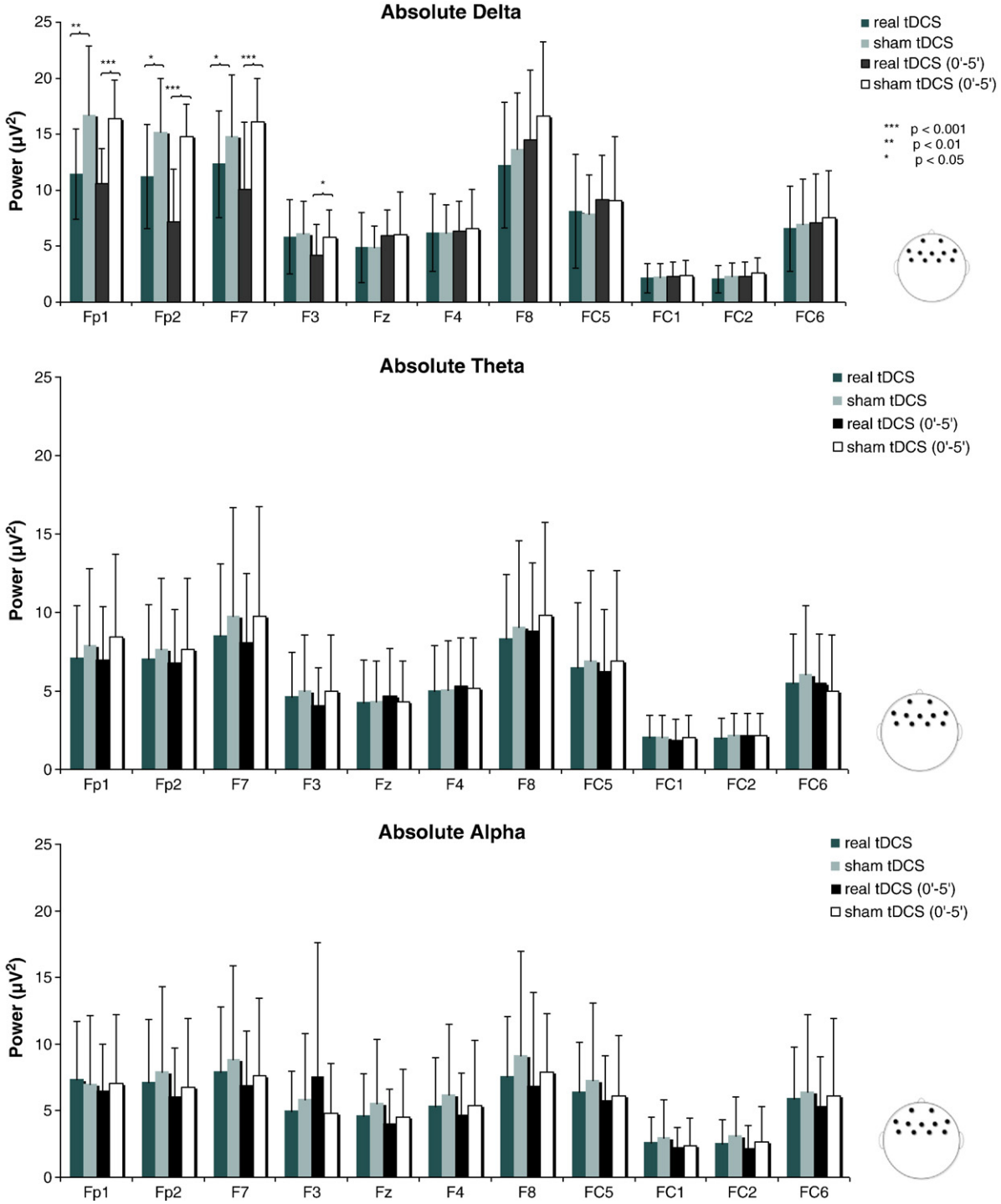

Fig. 2. Effect of real vs. sham tDCS on absolute power (μV^2) as a function of single frontal electrode comparisons for the frequency bands Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–30 Hz) and Gamma (30–40 Hz). Resting state EEG after real and sham tDCS is given for the frontal electrodes. The green bars show the whole mean EEG record (10 min), black and white bars represent the first 5 min (0′–5′) of EEG recording. The head in the lower corner right indicates the chosen electrodes. Even electrode numbers represent the right frontal hemisphere, odd numbers the left frontal hemisphere. Note tDCS was applied to the left DLPFC.

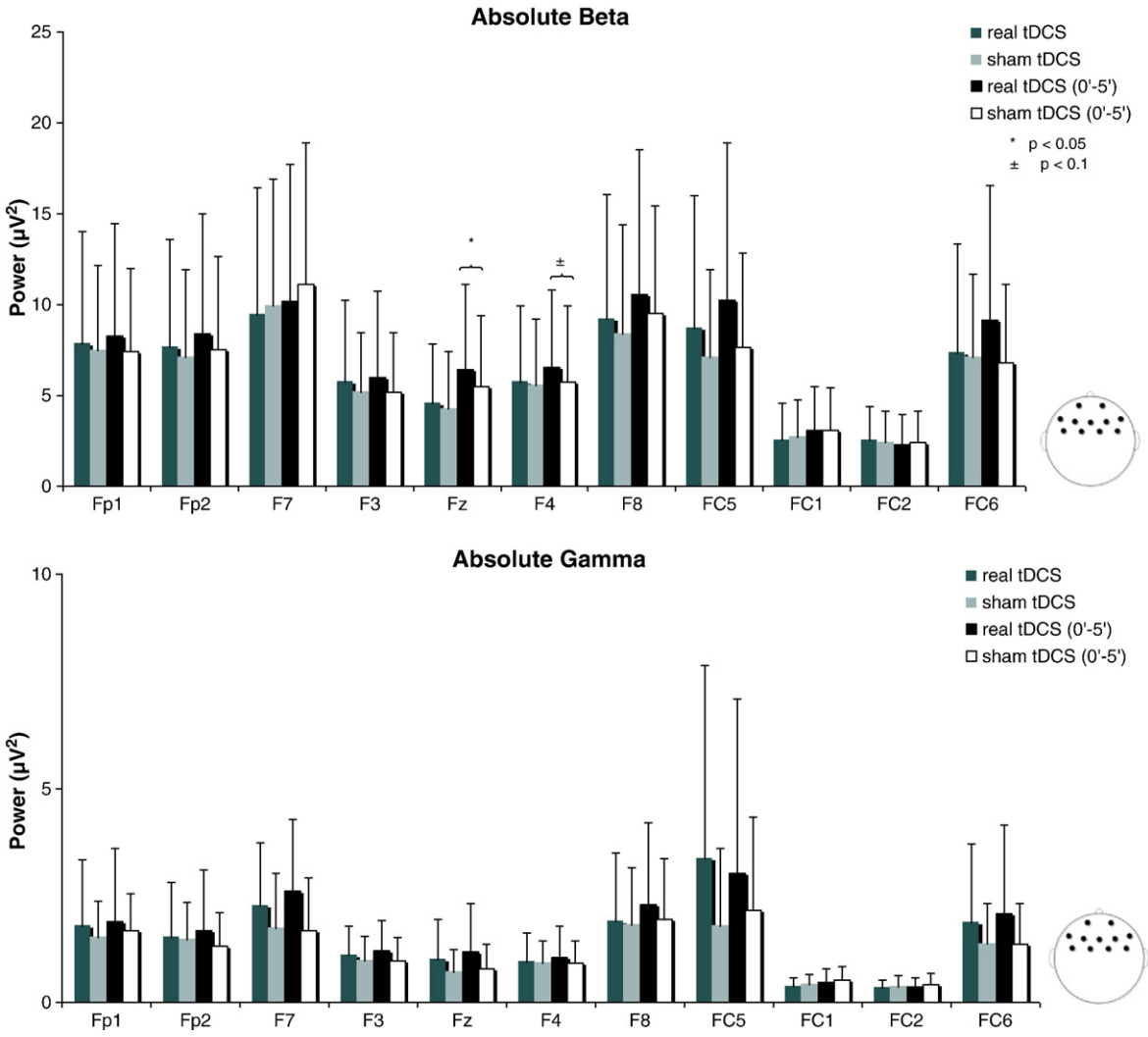

Fig. 2 (*continued*).

Table 2
Statistical non-parametric comparisons between current source density values of real vs. sham tDCS stimulations using sLORETA. Results for the delta- and beta-1-band activity.

	Region	XYZ (MNI)			Brodmann area	T-value
a) 0′–10′						
Real vs. sham	Medial frontal gyrus	−5	20	−20	25	−4.16*
	Subcallosal gyrus	−5	20	−15	25	−4.14*
	Anterior cingulate	−5	20	−10	32	−4.11*
	Medial frontal gyrus	−5	−25	−20	25	−4.06±
	Rectal gyrus	−10	20	−25	11	−4.01±
b) 0′–5′						
Delta	Anterior cingulate	−5	20	−5	25	−5.45**
	Anterior cingulate	−5	25	−5	24	−5.43**
	Anterior cingulate	−5	20	−10	32	−5.32**
	Anterior cingulate	−5	25	−10	32	−5.30**
	Subcallosal gyrus	−5	25	−15	25	−5.22
	Medial frontal gyrus	−6	20	−20	11	−5.13
beta	Cingulate gyrus	10	20	40	32	3.53±

0′–10′ = 10 min of EEG recording after tDCS.
0′–5′ = first 5 minutes of EEG recording (Note: for delta-band only t-values of $p<0.01$ are shown).
* p-value < 0.05.
± p-value < 0.10.
** p-value < 0.01.

according to the locations of the EEG generators. Eye artifacts pattern search was automatically performed. In the next step, the surrogate dipole model was combined with the source model of the eye artifact. After that the artifact was subtracted from the data.

ERP averaging

Corrected data were exported into Brain Vision Analyzer 1.05 (Brainproducts, Munich, Germany), re-referenced to common average after channels T01, T02, P09, P10 were excluded from further analysis. Then data were filtered (low pass filter 30 Hz, 48 dB/oct; high pass filter 0.53 Hz, 48 dB oct) and segmented (100 ms pre-stimulus baseline to 600 ms post stimulus). We analyzed all components at all channels and selected the P2- and P3-components for the electrodes Fz, Cz and Pz for further statistical analysis. This selection was done to restrict our analysis to a more global view on ERPs. As midline areas are well-known to show replicable components and activations during working memory tasks, P2- and P3- peak amplitudes were determined prior to analysis for the experimental conditions by defining the peak within a classified time window for P2 (100–250 ms after a stimulus) and P3 (260–400 ms after stimulus). All sweeps were automatically excluded from averaging if the voltage exceeded 70 ± μV in any of the 25 channels at any point during the averaging period.

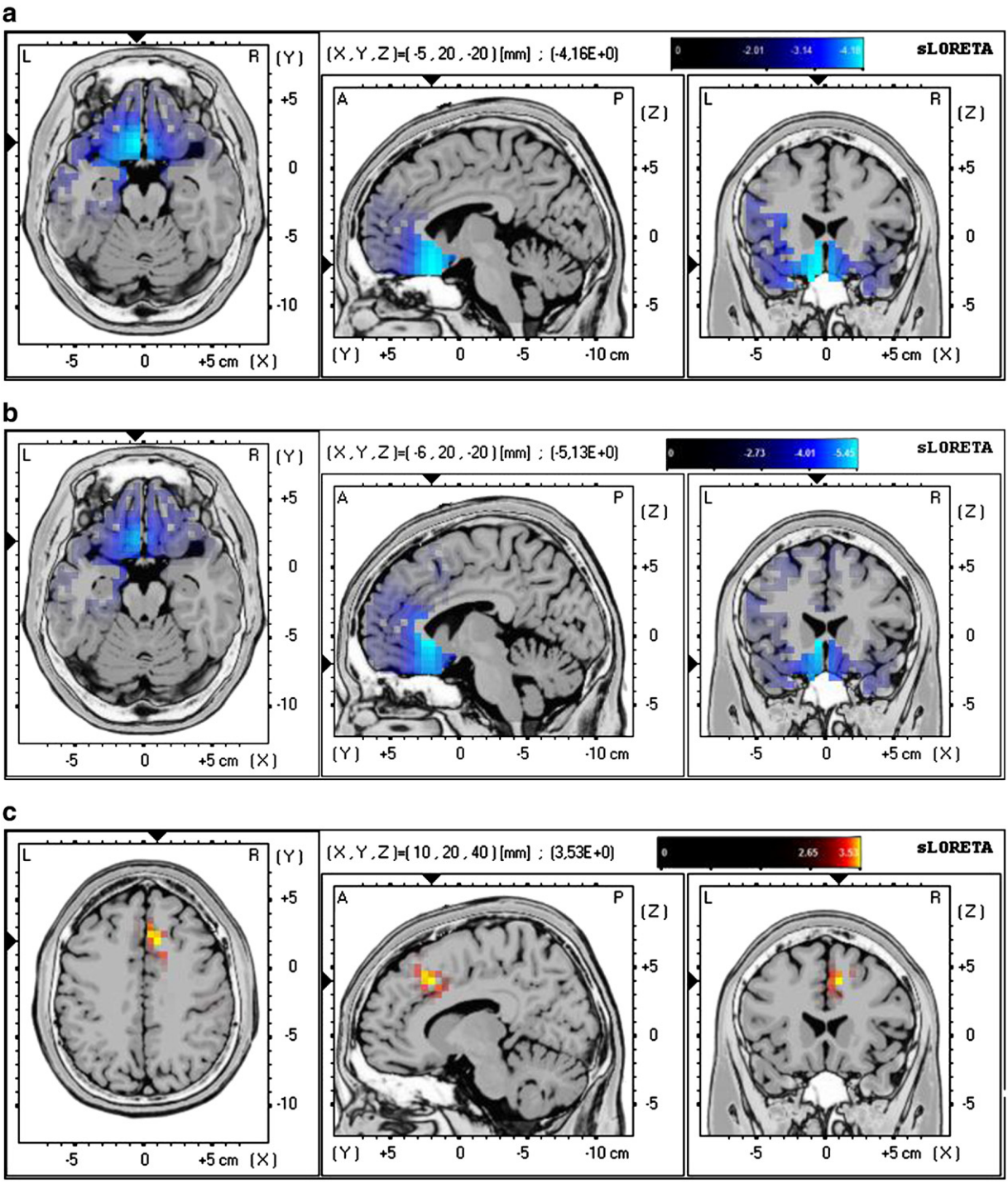

Fig. 3. The effect of real tDCS vs. sham tDCS on the mean current source density analyzed by sLORETA. a) for the whole resting-state EEG (10 min): a significant ($p<0.042$) reduction was detected for the deltaband (1–6.5 Hz) and localized in the subgenual prefrontal cortex (xyz = −5, 20, −20; BA 25). b) for the time period 0–5 min a significant ($p=0.001$; two-tailed) reduction was detected on the mean current source density analyzed by sLORETA. For the deltaband (1–6.5 Hz). The strongest effects were localized in the subgenual prefrontal cortex (xyz = −6, 20, −20; BA 25). c) for the time period 0–5 min a significant trend ($p<0.10$) was detected in the gyrus cingulate (xyz = 10,20,40; BA 32) of the beta 1 band (13–18 Hz). Note there was no significant difference in any other frequency band for the time period 5–10 min, indicating that real vs. sham tDCS had only a significant effect up to 15 min after stimulation and 5 min after EEG recording on the resting-state EEG.

sLORETA

To enhance the spatial sensitivity of our ERP procedure, we used the following time windows on the EEG source analysis: i) −150–50 ms ii) 50–250 ms iii) 260–450 ms and iv) 450–650 ms. We used all scalp electrodes in a source localization analysis using sLORETA. This was done separately for all 0-, 1- and 2-backs. The significance level was set to $p<0.10$ and $p<0.05$.

Statistics

We used analysis of variance for repeated measures (ANOVA) to investigate if there was a difference between real and sham tDCS. Data are reported as means and standard deviations. Mauchly's test was used to test for sphericity, and the Greenhouse–Geisser correction was applied if necessary. The Wilcoxon signed rank test (nonparametric test) was used for the ERP statistics because our sample was reduced to seven subjects due to artifacts. Given the exploratory character of the

Table 3
Changes in miss rate, accuracy, error rate and reaction time after real and sham tDCS.

	Baseline			Sham			Real		
n-back	0-back	1-back	2-back	0-back	1-back	2-back	0-back	1-back	2-back
Miss rate	0.05 ± 0.06	0.09 ± 0.06	0.18 ± 0.12	0.04 ± 0.05	0.12 ± 0.07	0.18 ± 0.11	0.04 ± 0.05	0.13 ± 0.10	0.20 ± 0.11
Accuracy	0.95 ± 0.06	0.85 ± 0.09	0.66 ± 0.17	0.95 ± 0.05	0.84 ± 0.10	0.67 ± 0.13	0.96 ± 0.05	0.83 ± 0.14	0.73 ± 0.13[ab]
Error rate	0.00 ± 0.00	0.05 ± 0.04	0.15 ± 0.09	0.03 ± 0.005	0.03 ± 0.03	0.14 ± 0.06	0.01 ± 0.004	0.04 ± 0.05	0.08 ± 0.06[ab]
Reaction time (ms)	523.5 ± 46.5	289.2 ± 43.0	568.0 ± 250.4	509.6 ± 57.2	294.2 ± 93.1	438.9 ± 163.7	463.2 ± 27.2 [ab]	253.4 ± 48.2[c]	386.5 ± 150.0[c]

Values are mean ± standard deviation.
[a]$p<0.05$ vs. baseline.
[b]$p<0.05$ vs. placebo.
[c]$p<0.10$ vs. baseline.

study, statistical significance levels were set to $p=0.05$ and $p<0.10$ (statistical trend) and not corrected for multiple comparisons. Correlations were calculated using Pearson's correlation coefficient with a significance level of $p<0.05$ and a statistical trend ($p<0.1$). All statistical analyses were performed using the SPSS 13.0 software (Statistical Package for Social Sciences, SPSS Inc, Chicago) or the implemented statistical sLORETA nonparametric mapping (SnPM) tool (Pascual-Marqui et al., 2002). The SnPM analysis tool includes a correction for multiple comparisons and does not require any assumption of Gaussianity (Diener et al., 2010).

Results

Distinguishability of DC stimulators

All subjects were asked if they perceived a difference between the stimulation conditions and if they could specifically discern real from placebo tDCS. Nobody was able to distinguish real and sham tDCS, nor did the reported sensations differ between stimulation conditions.

Mood changes

No side effects of stimulation were reported. There were no significant differences in the PANAS before and after tDCS (see Table 1). The Positive Affect Scale showed no main effects for time ($F(1,9)=0.02$, $p=0.96$, n.s.) and stimulation condition (anodal vs. sham) ($F(1,9)=0{,}11$, $p=0.75$, n.s.) nor for the interaction time x condition ($F(1,9)=1.99$; $p=0.19$, n.s.). On the Negative Affect Scale, there was no main effects for time ($F(1,9)=0.211$; $p=0.66$, n.s.), stimulation condition ($F(1,9)=0.01$, $p=0.91$, n.s.) and the interaction time x condition ($F(1,9)=0.64$; $p=0.44$, n.s.).

Single electrode comparisons

We conducted repeated-measures ANOVA for our main region of interest, i.e. the prefrontal cortex. A three-way repeated-measures ANOVA with condition (anodal, sham), lead (Fp1, Fp2, F7, F3, F4, F8, FC5, FC1, FC2, and FC6) and frequency band (delta, theta, alpha, beta, gamma) as within-subjects factors on the absolute EEG power revealed significant main effects of lead ($F(1.55,13.92)=40.21$, $p=0.0004$), condition x lead ($F(12.35,3,79)=7.66$, $p=0.019$), lead x frequency ($F(3.82,34.34)=16{,}94$, $p=0.0001$) and condition x frequency x lead ($F(3.82,34.39)=3.17$, $p=0.027$). Post-hoc ANOVAs for each frequency band showed that significant condition x lead interactions were found in the delta frequency band ($F(5,45)=9.84$, $p=0.001$). The EEG power at each lead for real and sham tDCS in the delta, theta, alpha, beta and gamma band are shown in Fig. 2. Prefrontal real tDCS induced a significant decrease in delta power at the Fp1, Fp2 and F7 electrodes (Fp1: $t(9)=-3.32$, $p=0.009$; Fp2: $t(9)=-2.47$, $p=0.036$; F7: $t(9)=-2.66$, $p=0.026$). Analysis of the first 5 min of EEG recording (0–5 min) identified a stronger main effect of lead ($F(1.51,13.60)=47.59$, $p=0.0002$), condition x lead ($F(4.4,39.55)=16.59$, $p=0.0009$), lead x frequency ($F(3.65,32.81)=7.78$, $p=0.0008$) and condition x frequency x lead ($F(4.39,39.50)=8.33$, $p=0.001$). We detected again a condition x lead interaction for the delta frequency band. Real tDCS decreased activity at the frontal leads Fp1, Fp2, F3 and F7 (Fp1: $t(9)=-8.49$, $p=0.0001$; Fp2: $t(9)=-5.5$, $p=0.0003$; F3: $t(9)=-3.15$, $p=0.01$; F7: $t(9)=-5.58$, $p=0.0003$) and a statistical trend was identified for FC5 (FC5: $t(9)=-2.05$, $p=0.07$). Additionally, prefrontal tDCS had an effect on the beta band where it significantly increased activity at Fz (Fz: $t(9)=2.31$, $p=0.046$) and F4 (F4: $t(9)=2.15$, $p=0.061$).

sLORETA results

In order to further localize the changes in delta activity, sLORETA was applied. SnPM showed a reduced left frontal delta (1–6.5 Hz) activity in the real tDCS condition compared to sham tDCS. Specifically, we detected a decrease in current densities (sLORETA) in real tDCS compared to sham tDCS for the delta band localized in the left subgenual PFC/medial frontal gyrus, Brodmann area, BA 25 ($t=-4.16$, $p<0.05$), in the subcallosal gyrus, BA 47($t=-4.14$, $p<0.05$), in the anterior cingulate (ACC), BA 32 ($t=-4.11$, $p<0.05$), in the medial frontal gyrus, BA 25 ($t=-4.06$, $p<0.10$) and in the left rectal gyrus, BA 11 ($t=-4.01$; $p<0.079$) (Table 2a, Fig. 3a). We did not find significant results for any other frequency band.

To further elucidate if there where any time effects we looked at the sLORETA time course. We found a strong statistical effect ($p<0.01$) in the delta band and a statistical trend ($p<0.10$) in the beta band when we analyzed the first 5 minutes of EEG recording (see Table 2b, Figs. 3b,c). There was not any significant effect or trend for the later time window 5–10 min. The strongest effect for the source localization was found in the subgenual PFC ($t=-5.13$, xyz = −6, 20, −20; BA 25) for the delta frequency (1–6.5 Hz). A statistical trend of increased activity was found in the rostral ACC ($t=3.53$, xyz = 5, 20, 40; BA 32) for the beta-1-band (13–18 Hz).

n-back task: behavioral results

We analyzed the different memory load of the n-back tasks (0-, 1-, 2-back) and all n-backs combined using a two-way repeated-measures ANOVA, with 'condition' (baseline, anodal, sham) and behavioral n-back subcategories for miss rate, accuracy, error rate, reaction time as within-subjects factor (see summary, Table 3). For the combined n-backs accuracy condition the analysis revealed that there were significant differences between condition ($F(2,18)=6.53$, $p=0.007$). Post-hoc analyses, with a Bonferroni correction for multiple comparisons, indicated that error rate was significantly lower after real tDCS ($M=0.04\pm0.03$) compared to sham tDCS ($M=0.06\pm0.03$), with $p=0.037$ and baseline assessment ($M=0.07\pm0.04$), with $p=0.027$. Analyzing results of the single n-back conditions, we found a significant effect between conditions only for 2-back ($F(2,18)=7.43$, $p=0.004$). There was a significant lower error rate in the 2-back task after real stimulation ($M=0.08\pm0.06$) in contrast to sham tDCS ($M=0.14\pm0.06$, $p=0.013$) and baseline ($M=0.15\pm0.09$, $p=0.018$), suggesting

that real tDCS especially influences error rate in conditions with higher memory load.

Additionally, real tDCS significantly reduced reaction time (M = 366.40 ± 57.1) as compared to baseline (M = 460.23 ± 95.3), ($F(2,18) = 8.70$, $p = 0.002$), but not to sham stimulation (M = 414.26 ± 82.6, $p = 0.19$). Comparison between the single n-backs revealed that there was a significant effect of condition for the 0-back ($F(2,18) = 11.17$, $p = 0.001$) and 2-back task ($F(2,18) = 8.70$, $p = 0.002$). Regarding the 0-back condition, real DC stimulation (M = 463.19 ± 27.2) reduced the reaction time significantly as compared to sham tDCS (M = 509.62 ± 57.2, $p = 0.006$) or baseline assessment (M = 523.49 ± 46.5, $p = 0.002$). For the 1-back condition, real tDCS (M = 253.38 ± 48.2) reduced reaction time only trendwise as compared to baseline performance (M = 289.2 ± 43.0;$p = 0.062$) but did not differ from sham tDCS (M = 294.23 ± 93.1). We found a similar result for the 2-back condition where we detected a significant effect for condition ($F(2,18) = 4.76$, $p = 0.022$), but only a statistical trend ($p = 0.084$) after real tDCS (M = 386.51 ± 150.0) vs. baseline (M = 567.99 ± 250.4) and no difference ($p = 0.19$) compared to sham tDCS (M = 438.94 ± 163.7).

Finally, there was a significant effect of condition for the 2-back accuracy ($F(2,18) = 4.97$, $p = 0.019$), driven by better accuracy after real stimulation (M = 0.73 ± 0.13) as post hoc contrasts showed that accuracy was significantly enhanced ($p = 0.024$) compared to sham stimulation (M = 0.67 ± 0.13) and non-significantly improved as compared to baseline performance (M = 0.66 ± 0.17, $p = 0.13$).

n-back task: ERP results

Three subjects were excluded from the analysis because of artifacts or due to ERP outliers. Table 4 shows ERP amplitudes and latencies for P2 and P3 amplitudes at midline electrodes (Fz, Cz and Pz).

Only in the 2-back task P2 potentials were significantly increased at electrode Fz after real DC stimulation (5.55 ± 1.45 μV) compared to sham (4.02 ± 1.51 μV, $p = 0.046$, Wilcoxon signed rank test) and baseline (3.62 ± 1.66 μV, $p = 0.018$, Wilcoxon signed rank test) conditions. After real tDCS we found a significantly reduced P2 latency (202 ± 32 ms, $p = 0.042$) at Cz compared to baseline. (Fig. 4c). All results incl. trends are shown in Table 4.

Only in the 2-back condition the P3 potentials were significantly higher at Fz after prefrontal stimulation (2.10 ± 1.05 μV) compared to sham stimulation (0.61 ± 0.81 μV, $p = 0.047$, Wilcoxon signed rank test). Two trends were found for increased voltage at Pz after real tDCS (9.58.61 ± 2.78 μV, $p = 0.063$, Wilcoxon signed rank test) for the 0-back condition if compared to baseline (8.12 ± 1.74 μV) and for the 2-back condition if real tDCS (7.64 ± 2.17 μV) was compared to baseline (6.63 ± 1.14 μV, $p = 0.084$ The latency after sham stimulation (328 ± 44 ms) compared to real tDCS (315 ± 23) at Cz showed a significant difference ($p = 0.027$, Wilcoxon signed rank test). All results are shown in Table 4.

Correlation of P2 and P3 results with memory performance after tDCS

Analyses of post-tDCS findings revealed no significant correlations between the P2-amplitude and miss rate, accuracy, error rate or reaction time.

Interestingly, Pearson linear correlation analysis showed a significant negative correlation between the P3 amplitude at electrode Pz and error rate for the 2-back condition ($r = -0.78$, $p = 0.04$) at baseline. In regard to higher memory effort (2-back) higher voltage at Pz was significantly associated with reduced error rate ($r = -0.79$, $p = 0.04$) and reduced reaction time ($r = -0.87$, $p = 0.011$) after prefrontal tDCS. These results are shown in Table S1 (Supporting Information).

Memory effect on sLORETA

We looked on the averaged ERPs within the time windows: −150 to 50 ms, 50–250 ms, 250 ms–450 ms and 450–650 ms for all 0-back, 1-back and 2-back separately. We did not find any significant effects for the 0-back and 1-back condition. For the 2-back condition there was a significant effect ($p < 0.05$, two-tailed) in the left parahippocampal gyrus ($t = 7.41$, xyz = −15, −3, −21; BA 35) for the time window 250–450 ms compared to sham tDCS (see Fig. 5).

Discussion

EEG study

Our results suggest that anodal tDCS above the left DLPFC with the cathode placed supraorbitally on the contralateral side may influence regional electrical activity in the surface EEG and deeper in the prefrontal lobe as revealed by sLORETA. However, the underlying mechanisms are not well understood and several hypotheses might be discussed, e.g. neuroplastic effects by prolonged weak depolarization/hyperpolarization, effects on connected networks or even brain conductivity heterogeneities.

As a matter of fact, other brain stimulation studies of the left DLPFC showed a similar modulation of regional brain activity in the subgenual PFC. In several studies combining rTMS with functional neuroimaging and magnetoencephalography (MEG) (Kimbrell et al., 1999; Maihofner et al., 2005; Speer et al., 2000), particularly slow magnetoencephalographic (MEG) activity (2–6 Hz) in the PFC decreased after rTMS of the left DLPFC (Maihöfner et al., 2005). Regarding brain stimulation studies of the primary motor cortex, anodal tDCS increased the rCBF in widespread cortical and subcortical areas as compared to cathodal tDCS, while cathodal stimulation entailed an excitability decrease of the metabolic activity in the corresponding areas (Lang et al., 2005). However, the strongest effects in that study were not seen in the motor cortex but in the supplementary motor area, suggesting large-scale network changes due to DC stimulation (Lang et al., 2005). Applying BOLD fMRI, Baudewig and colleagues found changes of cortical activity by not primarily in the areas under the tDCS electrodes (Baudewig et al., 2001), but rather in closely connected brain regions, suggesting a complex spatial distribution of the tDCS action. However, previous neuroimaging studies did not investigate possible tDCS effects on frontal brain regions. For tDCS-induced EEG alterations, it was shown that cathodal tDCS of the primary motor cortex increases slow-wave delta and theta EEG activity, while anodal stimulation reduces it, again also in regions outside the electrode placements (Ardolino et al., 2005). Another study has recently shown that anodal prefrontal compared to sham stimulation with 1 mA has an effect for up to 10 min after the end of stimulation on functional near-infrared spectroscopy (Merzagora et al., 2009). This is in line with our result showing that prefrontal stimulation with 2 mA had an impact on EEG activity for up to 15 min after the end of DC stimulation. Our results show that tDCS of the prefrontal cortex influences cortical dynamics in the frontal network with a pronounced activation in the medial frontal gyrus, the ACC and the subgenual cortex. These results are compatible with those of a recent prefrontal rTMS study that found a significant reduction of the PET binding potential in almost the same regions of the left DLPFC (BA 25, 11 and 32) after 10 Hz repetitive TMS stimulation (Cho and Strafella, 2009).

Amplitude increases in low frequency oscillations are related to a decreased BOLD signal in fMRI studies — hence an excitatory shift in neuronal activity from lower to higher frequencies would result in reduced delta and theta activity and increased beta and gamma amplitudes. Recently, reduced delta power and increased beta power were significantly ($r = -0.73$ and $r = 0.53$) correlated to increased functional connectivity in a simultaneous EEG-fMRI study (Hlinka et al., 2010). Here we provide further proof that a more alert state (may established via excitatory anodal Direct Current brain stimulation) leads to reduced delta power and increased beta power,

Table 4
Effects of real and sham tDCS on P2- and P3-ERP-components and latencies for the midline electrodes Fz, Cz, and Pz.

	Baseline									Sham			
n-back	0-back			1-back			2-back			0-back			1-back
electrode	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz
P2 – Voltage (μV)	3.51 ± 1.7	3.67 ± 1.7	none	3.73 ± 2.0	4.47 ± 1.5	4.74 ± 0.8	3.62 ± 1.7	none	none	3.62 ± 1.9	3.85 ± 1.6	none	3.91 ± 2.7
P2 – latency (ms)	180 ± 11	196 ± 37	none	178 ± 14	197 ± 29	228 ± 25	189 ± 14	none	none	179 ± 6	202 ± 37	none	182 ± 10
P3 – Voltage (μV)	1.91 ± 0.6	4.90 ± 1.5	8.12 ± 1.7	0.81 ± 1.0	3.6 ± 1.2	4.0 ± 2.6	0.81 ± 1.0	5.43 ± 1.6	6.63 ± 2.9	1.57 ± 1.6	4.79 ± 1.8	9.47 ± 1.4	1.10 ± 1.0
P3 – latency (ms)	385 ± 97	342 ± 25	322 ± 42	384 ± 83	359 ± 61	308 ± 80	359 ± 97	342 ± 27	313 ± 35	390 ± 111	350 ± 30	314 ± 12	385 ± 93

None = no component was detetected.
Values are mean ± standard deviation.
[a]$p<0.05$ vs. Baseline.
[b]$p<0.05$ vs. Sham.
[c]$p<0.10$ vs. Baseline.
[d]$p<0.10$ vs. Sham.

supporting the results of Hlinka and colleagues (Hlinka et al., 2010) on another experimental domain (non-invasive brain stimulation).

Our study provides first pilot data of tDCS-associated excitability changes within the DLPFC, extending the previous results of motor cortex tDCS studies induced (Nitsche et al., 2005).

Additionally, we found activations in a widespread area of the prefrontal cortex that could play an important role in revealing the functional anatomy of effects induced by prefrontal tDCS. In summary, existing neuroimaging, TMS and EEG studies support the hypothesis that tDCS alters the level of neural excitability (Nitsche et al., 2003a, 2002, 2005; Nitsche and Paulus, 2000).

On a functional level we did not find an immediate influence of prefrontal tDCS on mood. The results in the PANAS questionnaire did not differ between real and sham stimulation. These data are consistent with a previous study of Koenigs et al. 2009 that did not find any significant mood effects of bifrontal tDCS in a double-blind crossover study where participants underwent a single session of anodal, sham and cathodal tDCS (Koenigs et al., 2009).

The finding that prefrontal tDCS particularly modulates delta activity in the medial frontal cortex, the ACC and the subgenual cortex (SGC) of healthy subjects could form a link to previously reported effects of prefrontal tDCS on depression, risk taking behavior, impulsiveness, pain modulation and craving (Beeli et al., 2008a,b; Boggio et al., 2008b; Fecteau et al., 2007a,b).

The SGC, where we observed the strongest effect of anodal tDCS (BA 25), plays a central role in the neurobiology of depression and affective disorders (Hajek et al., 2008). Neuroimaging studies reveal an interaction between changes of regional brain activity in this area and the severity of depression (Drevets et al., 2002; Hajek et al., 2008; Pizzagalli et al., 2004), although the direction of these changes does vary across methodologies and patient populations (Hajek et al., 2008; Mayberg et al., 2000, 2005).

Using LORETA, two previous studies demonstrated an increase of delta activity in the subgenual PFC in patients with major depression (Pae et al., 2003; Pizzagalli et al., 2001, 2004). Moreover, Pizzagalli et al. (2004) reported that EEG delta-activity tended to decrease in the subgenual PFC of melancholic subjects in contrast to non-melancholic subjects after antidepressant treatment, as demonstrated by LORETA. Thus, one might speculate that the antidepressant effect of anodal tDCS above the left DLPFC and right cathodal tDCS supraorbitally reported elsewhere (Boggio et al., 2008a; Ferrucci et al., 2009; Fregni et al., 2006; Rigonatti et al., 2008) may be mediated by the tDCS effects on the SGC observed here. Furthermore, a recent study revealed that nucleus accumbens (NAcc) responses were inversely associated with rostral ACC resting delta activity and the authors mentioned that available animal data suggest that dopamine release in the NAcc is associated with decreased delta activity (Wacker et al., 2009). Cho and Straffela also provided first evidence of extrastriatal dopamine modulation in the subgenual and orbitofrontal cortex following acute rTMS of the left DLPFC (Cho and Strafella, 2009). McCormick and colleagues found that a normalization of subgenual theta activity after electroconvulsive therapy was associated with decreased psychotic symptoms in patients with depression and psychotic disorders (McCormick et al., 2009).

Our sLORETA results could also be interpreted in a way that the pain system is modulated by prefrontal tDCS, as pilot data indicate a significant increase of pain thresholds after prefrontal tDCS, and the ventral and rostral area of the ACC has a predominant role in endogenous pain control (Boggio et al., 2008b).

Several methodological considerations are necessary. Firstly, we found a significant effect in the delta spectral power and a statistical trend in the beta-1-band in the source analysis of areas in the prefrontal cortex. Whereas the values in the delta band are clearly significant we found only a statistical trend in the beta band. However, we measured the EEG approximately 10 min after tDCS stimulation and this time lag may have contributed to the lesser effect on the EEG. This assumption is further confirmed by the fact that the EEG analysis of the whole time window (10 min) showed weaker statistical results than the first 5 min.

Secondly, our sample size was relatively small. Acknowledging the limited spatial resolution and precision of sLORETA, it must be pointed out that our findings are preliminary and functional imaging techniques with more precise localization (e.g. fMRI or PET) are needed in order to confirm our present results.

n-back behavioral results

In addition to EEG, we introduced a working memory (n-back) paradigm in this experiment to obtain behavioral data as positive control for our EEG findings. Indeed, prefrontal tDCS enhanced performance in the n-back-task. It is important to emphasize that the task was carried out not immediately, but 20–40 min after tDCS. Our findings are in line with a prior study looking on a verbal memory n-back task after prefrontal tDCS revealing a significant change in accuracy 30 min after completing tDCS (Ohn et al., 2008). Different to this previous study (Ohn et al., 2008) we used a non-verbal n-back task and stimulated with 2 mA for 20 min whereas Ohn et al. stimulated with 1 mA for 30 min. In contrast to previous studies (Fregni et al., 2005; Ohn et al., 2008) we found significant effects on the reaction time after prefrontal stimulation. This is in accordance with early work on frontal DC stimulation that found enhanced response speed in a simple reaction paradigm after anodal stimulation of the vertex, a region more posterior compared to our stimulation site but still within the frontal brain (Elbert et al., 1981). Nitsche and colleagues found that anodal stimulation of the primary motor cortex of healthy subjects resulted in reduced RTs in implicit motor learning (Nitsche et al., 2003d). In contrast, other studies could not detect any effect on reaction time (Fregni et al., 2005) or even found a worsening

					Real								
		2-back			0-back			1-back			2-back		
Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
4.5 ± 1.0	5.45 ± 1.5	4.02 ± 1.5	none	none	↑4.11 ± 2.1[c]	3.70 ± 1.4	none	3.85 ± 1.8	5.11 ± 2.1	5.25 ± 1.2	↑5.55 ± 1.5[a,b]	none	none
204 ± 29	228 ± 31	187 ± 13	none	none	181 ± 9	200 ± 37	none	178 ± 6	↓202 ± 32[a]	221 ± 31	190 ± 22	none	none
4.44 ± 2.5	4.31 ± 2.8	0.61 ± 0.8	5.54 ± 1.9	7.14 ± 2.2	2.0 ± 0.9	5.46 ± 1.4	↑9.58 ± 2.8[c]	1.28 ± 1.0	4.1 ± 2.2	4.62 ± 2.6	↑2.1 ± 1.1[b,c]	5.88 ± 1.6	↑7.64 ± 2.2 [c]
373 ± 101	310 ± 47	360 ± 120	340 ± 23	328 ± 4	390 ± 91	333 ± 26	313 ± 29	382 ± 92	366 ± 90	304 ± 42	361 ± 97	340 ± 23	↓315 ± 4[d]

(Marshall et al., 2005). As Elbert and colleagues detected an RT-interaction only in the second half of their experiment we speculate about the possibility that the effects of prolonged weak tDCS might had a delayed effect on the domain of behavioral reaction time. This view might be supported by reports that found higher task accuracy and faster reaction times in later repeated sessions (Dockery et al., 2009) suggesting a possible strengthening of connections in time course. In addition, prefrontal tDCS was associated with improved reaction time in naming processing (Fertonani et al., 2010; Fiori et al., 2010) and in probalistic learning (Hecht et al., 2010).

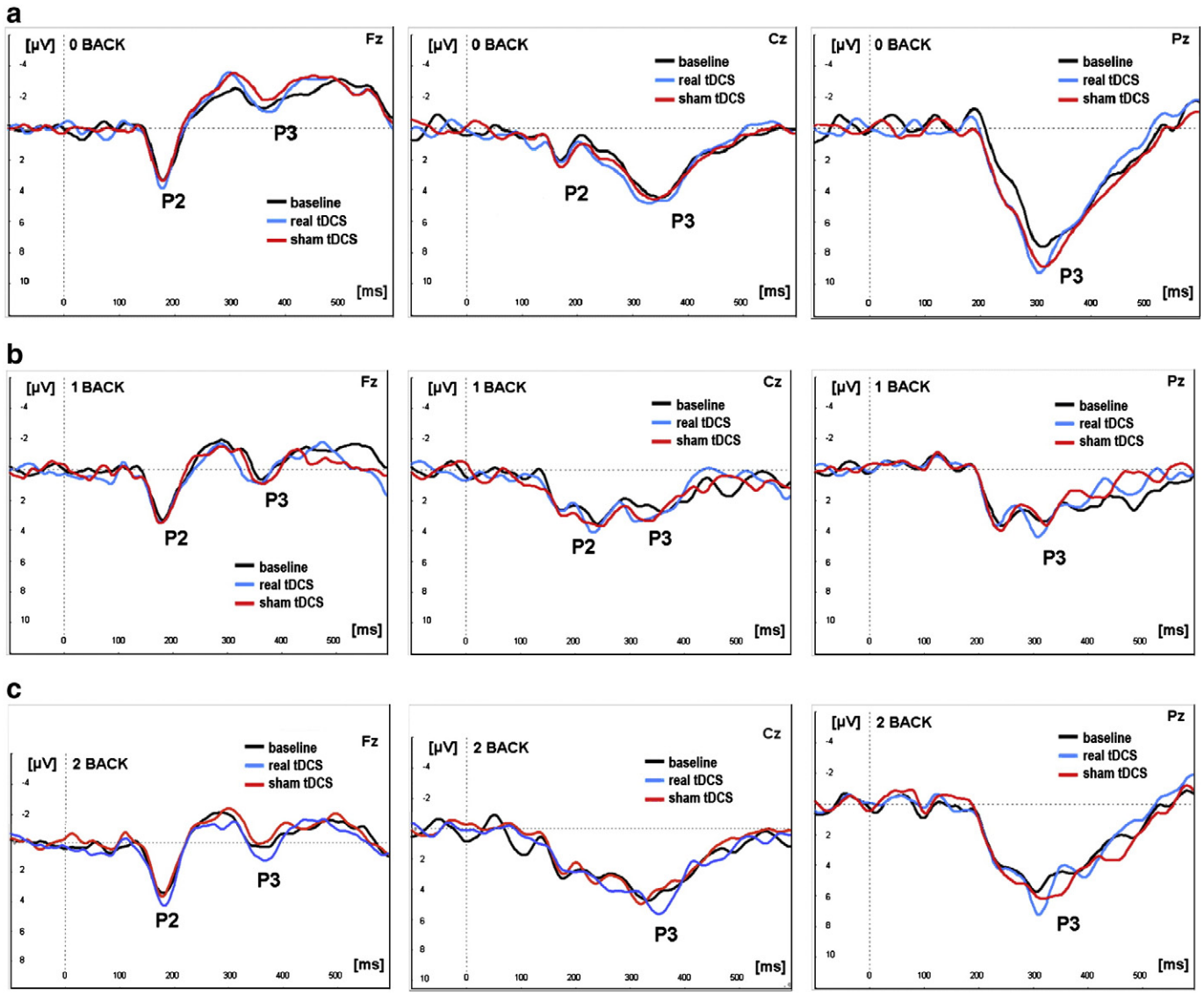

Fig. 4. ERP group averages for the n-back tasks. Here shown for the conditions baseline, real and sham for the midline electrodes Fz, Cz, Pz, time-window: 100 ms pre-stimulus baseline to 600 ms post stimulus. a) 0-back. b) 1-back. c) 2-back.

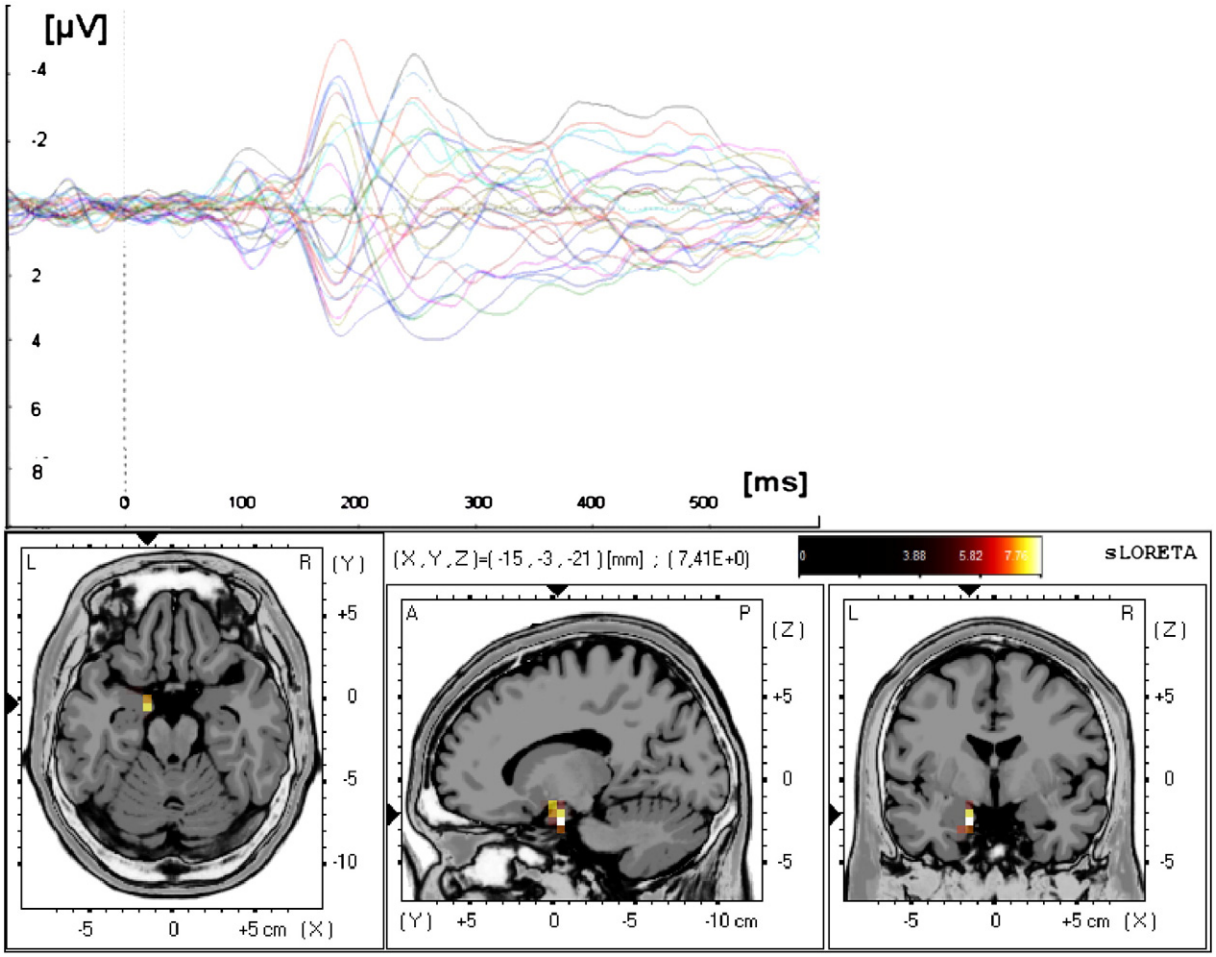

Fig. 5. sLORETA source localisation of 2-back memory retrieval as compared by real vs. sham tDCS. All electrodes were used for the source localisation in the time window 250–450 ms post-stimulus, see picture above for the baseline activations. Statistical comparison shows that the maximal activation stimulus appears in the left parahippocampal gyrus (xyz = −15, −3, −21; BA 35) on a significant level of $p<0.05$.

Furthermore, we observed an effect of prefrontal tDCS especially on the 2-back task. Correspondingly, several studies in the past found stronger activations of functional brain processes on higher working memory load (Braver et al., 1997; Callicott et al., 1999). Real tDCS of the prefrontal cortex seems to influence the accuracy and error rate for higher memory load (2-back), whereas it reduces the reaction time especially in the lower memory load (0-back) condition. We suggest that Direct Current (DC) stimulation prior to task condition contributed to increased efficient network dynamics more capable of higher task demands, whereas it seems to increase RTs on lower memory — load tasks that are more automatically processed.

n-back ERP study results

As expected, we found an influence of tDCS on ERPs during the n-back task.

P2: We found an increase of P2 amplitudes at Fz after real tDCS compared to sham and baseline conditions for the 2-back task. Increased P2 amplitudes have previously been associated with demanding memory load (Klaver et al., 1999).

P3: The amplitudes of P3 showed a significant increase at Fz after real tDCS compared to sham tDCS and baseline during the 2-back condition. This suggests that prefrontal real tDCS contributed to the P3-amplitude increase as it is known that structures such as the DLPFC and the anterior cingulate cortex, among other regions, are involved in the generation of the P3-component (Benar et al., 2007; Halgren et al., 1998; Menon et al., 1997; Mulert et al., 2004). As we found modified activity in parts of these structures after prefrontal tDCS or during the n-back task as shown by sLORETA, it is possible that prefrontal tDCS is directly related to this increase of the P3 amplitude. While the P3 component is produced by a distributed network of brain processes associated with attention and memory operations, it is observed in any task that requires stimulus discrimination. It has been suggested recently that the P3 component could occur from the initial need to enhance focal attention during stimulus detection relative to the contents of working memory (Polich, 2007).

In our examination of memory recall in the 2-back condition by sLORETA we detected significant higher activation of the left parahippocampal gyrus after real tDCS. This effect was found between 250 and 450 ms post stimulus, whereas there was no significant difference in other latency periods. These results could be interpreted to mean that prefrontal tDCS influences the frontal cortex via fronto-hippocampal and fronto-parietal connections, as we see increased frontal and parietal activations after prefrontal tDCS. Past studies have found direct neuronal activity between the medial prefrontal cortex and the hippocampus in rodents during spatial working memory tasks (Jones and Wilson, 2005; Siapas et al., 2005) and there is evidence for a fronto-parietal network (Laufs, 2008; van den Heuvel et al., 2009). One major effect of the parahippocampal activation might be the updating of the working memory processes, as this region is well-known for its role in episodic memory (Johnson et al., 2008; Kumari et al., 2003; Ramsoy et al., 2009). Reciprocal connections between the dorsolateral prefrontal cortex (including the ACC) and the parahippocampal region are known (Goldman-Rakic et al., 1984). Assuming a

higher order network that mediates memory processes, tDCS might influence the whole network during the resting state period, making it easier to get the network activated during consecutive task performance. The role of the parahippocampal gyrus could be the representation activation of the cardinal numbers during memory delays (2-back). Hence, the stronger activity in the parahippocampal gyrus would explain the significant better accuracy and miss rate after real compared to sham stimulation.

An interesting finding of this study is the delayed impact of DC stimulation on the EEG. It seems that prefrontal tDCS directly influenced neuronal activity in the resting state for a certain time period, and might have kept the network more activated explaining the subsequent better performance and increased cognitive ERP amplitudes during the higher memory requirement of the 2-back task. There was consistency between improved behavioral performance and increased ERP amplitudes for the 2-back condition. Moreover shorter latencies may indicate reduced reaction time in the n-back task. Since tDCS stimulation affected the Fz- and Pz-electrode a strengthening of the frontal to parietal connectivity by real tDCS is possible. During rest we found increased high-frequency EEG activity in the gyrus cingulate. It is plausible that prefrontal tDCS induces activity changes in a broader network via top-down modulation starting at frontal cortical structures.

Thus, our results are in line with previous studies showing an effect of prefrontal tDCS on n-back tasks in healthy subjects (Fregni et al., 2005; Ohn et al., 2008) and in neurological/psychiatric patients (Boggio et al., 2006; Jo et al., 2009; Kang et al., 2009).

Previous studies did not differentiate between single n-backs and might have missed the effect of prefrontal tDCS on memory load. Other authors have reported effects on additional memory categories (Elmer et al., 2009; Kincses et al., 2004; Marshall et al., 2004), as well as on other cognitive domains (Cerruti and Schlaug, 2009; Dockery et al., 2009; Elmer et al., 2009; Fecteau et al., 2007a; Fertonani et al., 2010; Fiori et al., 2010; Iyer et al., 2005; Marshall et al., 2006; Palm et al., 2009; Priori et al., 2008; Sparing et al., 2007; Wassermann and Grafman, 2005). In summary our findings suggest that prefrontal tDCS influences and accelerates cortical EEG activity and may thus help explain the recently reported broad range of behavioral tDCS effects.

Limitations

One limiting aspect of our study is the small sample size and time-delay for the cognitive task. Due to these facts and the exploratory nature of our n-back study, we did not correct for multiple comparisons and might hereby have increased the possibility of type II errors. At the same time the risk of type I error was decreased, taking the preliminary character of our n-back study into account. Upcoming studies must corroborate our results. We also like to mention that we did not control for the hormonal status of our female subjects. Despite the pseudorandomized order and the cross-over design it might be criticized that we only performed baseline n-back on a separate day once and not before each experimental condition.

Another limitation is the lack of varying and controlling active electrode positions. The bipolar electrode positions may have resulted in effective stimulation of two brain regions. In addition to anodal tDCS of the left DLPFC, the right frontopolar cortex was stimulated with cathodal tDCS. In our study we used the electrode size of 7×5 cm^2 as most behavioral and clinical prefrontal tDCS studies up to date have used these electrode sizes. A neurobiological interpretation is complicated by two possible stimulation sources (anode/cathode). Future studies may encounter this important topic by increasing electrode size to reduce the effects of anode/cathode electrode or to use an extracephalic region (Vandermeeren et al., 2010).

Safety aspects

Finally, tDCS was well tolerated and the only side effect reported was an initial itching sensation. Previously reported skin lesions occurring after a longer clinical trial (5 days later) were not observed (Palm et al., 2008). This is in line with other previously conducted safety studies (Iyer et al., 2005; Poreisz et al., 2007; Tadini et al., 2010) and there have not been any reports of skin lesions for single 2 mA sessions.

Conclusion

In conclusion, we have shown that anodal/cathodal tDCS of the left DLPFC/right frontopolar region increases neuronal activation, corroborated by EEG results showing decreased localized delta-theta and enhanced beta activity both associated with a more alert state (Barry et al., 2009; Kilner et al., 2005) and increased functional connectivity (Hlinka et al., 2010).We further speculate that the increased activation in the prefrontal region and parahippocampal area led to the improvement in the n-back task. Combining tDCS and EEG should further contribute to our understanding of the neurophysiological mechanisms underlying the action of tDCS on behavioral measures. Given the likely effects on various cognitive and affective domains, prefrontal tDCS might have an impact in many clinical fields.

Supplementary materials related to this article can be found online at doi:10.1016/j.neuroimage.2010.12.004.

Acknowledgments

This study is part of the Ph.D. thesis of Daniel Keeser at the Faculty of Medicine of the Ludwig-Maximilians University of Munich (in preparation). We gratefully acknowledge T. Sprenger for his invaluable advise, and thank M. Hartmann, D. Bars und H.J. Engelbregt for critically reading our manuscript.

References

Ardolino, G., Bossi, B., Barbieri, S., Priori, A., 2005. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. J. Physiol. 568, 653–663.

Barry, R.J., Clarke, A.R., Johnstone, S.J., Brown, C.R., 2009. EEG differences in children between eyes-closed and eyes-open resting conditions. Clin. Neurophysiol. 120, 1806–1811.

Baudewig, J., Nitsche, M.A., Paulus, W., Frahm, J., 2001. Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. Magn. Reson. Med. 45, 196–201.

Beeli, G., Casutt, G., Baumgartner, T., Jancke, L., 2008a. Modulating presence and impulsiveness by external stimulation of the brain. Behav. Brain Funct. 4, 33.

Beeli, G., Koeneke, S., Gasser, K., Jancke, L., 2008b. Brain stimulation modulates driving behavior. Behav. Brain Funct. 4, 34.

Benar, C.G., Schon, D., Grimault, S., Nazarian, B., Burle, B., Roth, M., Badier, J.M., Marquis, P., Liegeois-Chauvel, C., Anton, J.L., 2007. Single-trial analysis of oddball event-related potentials in simultaneous EEG-fMRI. Hum. Brain Mapp. 28, 602–613.

Boggio, P.S., Ferrucci, R., Rigonatti, S.P., Covre, P., Nitsche, M., Pascual-Leone, A., Fregni, F., 2006. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J. Neurol. Sci. 249, 31–38.

Boggio, P.S., Bermpohl, F., Vergara, A.O., Muniz, A.L., Nahas, F.H., Leme, P.B., Rigonatti, S.P., Fregni, F., 2007. Go-no-go task performance improvement after anodal transcranial DC stimulation of the left dorsolateral prefrontal cortex in major depression. J. Affect. Disord. 101, 91–98.

Boggio, P.S., Rigonatti, S.P., Ribeiro, R.B., Myczkowski, M.L., Nitsche, M.A., Pascual-Leone, A., Fregni, F., 2008a. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int. J. Neuropsychopharmacol. 11, 249–254.

Boggio, P.S., Zaghi, S., Lopes, M., Fregni, F., 2008b. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur. J. Neurol. 15, 1124–1130.

Boggio, P.S., Zaghi, S., Fregni, F., 2009. Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia 47, 212–217.

Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E., Noll, D.C., 1997. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5, 49–62.

Callicott, J.H., Mattay, V.S., Bertolino, A., Finn, K., Coppola, R., Frank, J.A., Goldberg, T.E., Weinberger, D.R., 1999. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cereb. Cortex 9, 20–26.
Cerruti, C., Schlaug, G., 2009. Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. J. Cogn. Neurosci. 21, 1980–1987.
Cho, S.S., Strafella, A.P., 2009. rTMS of the left dorsolateral prefrontal cortex modulates dopamine release in the ipsilateral anterior cingulate cortex and orbitofrontal cortex. PLoS ONE 4, e6725.
Diener, C., Kuehner, C., Flor, H., 2010. Loss of control during instrumental learning: a source localization study. Neuroimage 50, 717–726.
Dockery, C.A., Hueckel-Weng, R., Birbaumer, N., Plewnia, C., 2009. Enhancement of planning ability by transcranial direct current stimulation. J. Neurosci. 29, 7271–7277.
Drevets, W.C., Bogers, W., Raichle, M.E., 2002. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. Eur. Neuropsychopharmacol. 12, 527–544.
Elbert, T., Lutzenberger, W., Rockstroh, B., Birbaumer, N., 1981. The influence of low-level transcortical DC-currents on response speed in humans. Int. J. Neurosci. 14, 101–114.
Elmer, S., Burkard, M., Renz, B., Meyer, M., Jancke, L., 2009. Direct current induced short-term modulation of the left dorsolateral prefrontal cortex while learning auditory presented nouns. Behav. Brain Funct. 5, 29.
Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., Pascual-Leone, A., 2007a. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. J. Neurosci. 27, 12500–12505.
Fecteau, S., Pascual-Leone, A., Zald, D.H., Liguori, P., Theoret, H., Boggio, P.S., Fregni, F., 2007b. Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. J. Neurosci. 27, 6212–6218.
Ferrucci, R., Mameli, F., Guidi, I., Mrakic-Sposta, S., Vergari, M., Marceglia, S., Cogiamanian, F., Barbieri, S., Scarpini, E., Priori, A., 2008. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. Neurology 71, 493–498.
Ferrucci, R., Bortolomasi, M., Vergari, M., Tadini, L., Salvoro, B., Giacopuzzi, M., Barbieri, S., Priori, A., 2009. Transcranial direct current stimulation in severe, drug-resistant major depression. J. Affect. Disord. 118, 215–219.
Fertonani, A., Rosini, S., Cotelli, M., Rossini, P.M., Miniussi, C., 2010. Naming facilitation induced by transcranial direct current stimulation. Behav. Brain Res. 208, 311–318.
Fiori, V., Coccia, M., Marinelli, C.V., Vecchi, V., Bonifazi, S., Ceravolo, M.G., Provinciali, L., Tomaiuolo, F., Marangolo, P., 2010. Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic subjects. J. Cogn. Neurosci. doi:10.1162/jocn.2010.21579.
Fregni, F., Boggio, P.S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M.A., Rigonatti, S.P., Silva, M.T., Paulus, W., Pascual-Leone, A., 2005. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp. Brain Res. 166, 23–30.
Fregni, F., Boggio, P.S., Nitsche, M.A., Marcolin, M.A., Rigonatti, S.P., Pascual-Leone, A., 2006. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord. 8, 203–204.
Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F.A., Nitsche, M.A., Mecca, T., Macedo, E.C., Pascual-Leone, A., Boggio, P.S., 2008. Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. Appetite 51, 34–41.
Goldman-Rakic, P.S., Selemon, L.D., Schwartz, M.L., 1984. Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. Neuroscience 12, 719–743.
Hajek, T., Kozeny, J., Kopecek, M., Alda, M., Hoschl, C., 2008. Reduced subgenual cingulate volumes in mood disorders: a meta-analysis. J. Psychiatry Neurosci. 33, 91–99.
Halgren, E., Marinkovic, K., Chauvel, P., 1998. Generators of the late cognitive potentials in auditory and visual oddball tasks. Electroencephalogr. Clin. Neurophysiol. 106, 156–164.
Hecht, D., Walsh, V., Lavidor, M., 2010. Transcranial direct current stimulation facilitates decision making in a probabilistic guessing task. J. Neurosci. 30, 4241–4245.
Hlinka, J., Alexakis, C., Diukova, A., Liddle, P.F., Auer, D.P., 2010. Slow EEG pattern predicts reduced intrinsic functional connectivity in the default mode network: an inter-subject analysis. Neuroimage 53, 239–246.
Iyer, M.B., Mattu, U., Grafman, J., Lomarev, M., Sato, S., Wassermann, E.M., 2005. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 64, 872–875.
Jaspers, H.H., 1958. The ten twenty electrode system of the international federation. Electroencephalogr. Clin. Neurophysiol. 10, 371–375.
Jo, J.M., Kim, Y.H., Ko, M.H., Ohn, S.H., Joen, B., Lee, K.H., 2009. Enhancing the working memory of stroke patients using tDCS. Am. J. Phys. Med. Rehabil. 88, 404–409.
Johnson, J.D., Muftuler, L.T., Rugg, M.D., 2008. Multiple repetitions reveal functionally and anatomically distinct patterns of hippocampal activity during continuous recognition memory. Hippocampus 18, 975–980.
Jones, M.W., Wilson, M.A., 2005. Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. PLoS Biol. 3, e402.
Kang, E.K., Baek, M.J., Kim, S., Paik, N.J., 2009. Non-invasive cortical stimulation improves post-stroke attention decline. Restor. Neurol. Neurosci. 27, 645–650.
Kilner, J.M., Mattout, J., Henson, R., Friston, K.J., 2005. Hemodynamic correlates of EEG: a heuristic. Neuroimage 28, 280–286.
Kimbrell, T.A., Little, J.T., Dunn, R.T., Frye, M.A., Greenberg, B.D., Wassermann, E.M., Repella, J.D., Danielson, A.L., Willis, M.W., Benson, B.E., Speer, A.M., Osuch, E., George, M.S., Post, R.M., 1999. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. Biol. Psychiatry 46, 1603–1613.
Kincses, T.Z., Antal, A., Nitsche, M.A., Bartfai, O., Paulus, W., 2004. Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. Neuropsychologia 42, 113–117.
Klaver, P., Smid, H.G., Heinze, H.J., 1999. Representations in human visual short-term memory: an event-related brain potential study. Neurosci. Lett. 268, 65–68.
Knoch, D., Nitsche, M.A., Fischbacher, U., Eisenegger, C., Pascual-Leone, A., Fehr, E., 2008. Studying the neurobiology of social interaction with transcranial direct current stimulation —the example of punishing unfairness. Cereb. Cortex 18, 1987–1990.
Koenigs, M., Ukueberuwa, D., Campion, P., Grafman, J., Wassermann, E., 2009. Bilateral frontal transcranial direct current stimulation: failure to replicate classic findings in healthy subjects. Clin. Neurophysiol. 120, 80–84.
Kumari, V., Gray, J.A., ffytche, D.H., Mitterschiffthaler, M.T., Das, M., Zachariah, E., Vythelingum, G.N., Williams, S.C., Simmons, A., Sharma, T., 2003. Cognitive effects of nicotine in humans: an fMRI study. Neuroimage 19, 1002–1013.
Lang, N., Siebner, H.R., Ward, N.S., Lee, L., Nitsche, M.A., Paulus, W., Rothwell, J.C., Lemon, R.N., Frackowiak, R.S., 2005. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? Eur. J. Neurosci. 22, 495–504.
Laufs, H., 2008. Endogenous brain oscillations and related networks detected by surface EEG-combined fMRI. Hum. Brain Mapp. 29, 762–769.
Liebetanz, D., Nitsche, M.A., Tergau, F., Paulus, W., 2002. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain 125, 2238–2247.
Maihöfner, C., Ropohl, A., Reulbach, U., Hiller, M., Elstner, S., Kornhuber, J., Sperling, W., 2005. Effects of repetitive transcranial magnetic stimulation in depression: a magnetoencephalographic study. NeuroReport 16, 1839–1842.
Marshall, L., Molle, M., Hallschmid, M., Born, J., 2004. Transcranial direct current stimulation during sleep improves declarative memory. J. Neurosci. 24, 9985–9992.
Marshall, L., Molle, M., Siebner, H.R., Born, J., 2005. Bifrontal transcranial direct current stimulation slows reaction time in a working memory task. BMC Neurosci. 6, 23.
Marshall, L., Helgadottir, H., Molle, M., Born, J., 2006. Boosting slow oscillations during sleep potentiates memory. Nature 444, 610–613.
Mayberg, H.S., Brannan, S.K., Tekell, J.L., Silva, J.A., Mahurin, R.K., McGinnis, S., Jerabek, P.A., 2000. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol. Psychiatry 48, 830–843.
Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Schwalb, J.M., Kennedy, S.H., 2005. Deep brain stimulation for treatment-resistant depression. Neuron 45, 651–660.
McCormick, L.M., Yamada, T., Yeh, M., Brumm, M.C., Thatcher, R.W., 2009. Antipsychotic effect of electroconvulsive therapy is related to normalization of subgenual cingulate theta activity in psychotic depression. J. Psychiatr. Res. 43, 553–560.
Menon, V., Ford, J.M., Lim, K.O., Glover, G.H., Pfefferbaum, A., 1997. Combined event-related fMRI and EEG evidence for temporal–parietal cortex activation during target detection. NeuroReport 8, 3029–3037.
Merzagora, A.C., Foffani, G., Panyavin, I., Mordillo-Mateos, L., Aguilar, J., Onaral, B., Oliviero, A., 2009. Prefrontal hemodynamic changes produced by anodal direct current stimulation. Neuroimage 49, 2304–2310.
Mulert, C., Jager, L., Schmitt, R., Bussfeld, P., Pogarell, O., Moller, H.J., Juckel, G., Hegerl, U., 2004. Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. Neuroimage 22, 83–94.
Nitsche, M.A., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol. 527 (Pt 3), 633–639.
Nitsche, M.A., Paulus, W., 2001. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57, 1899–1901.
Nitsche, M.A., Liebetanz, D., Tergau, F., Paulus, W., 2002. Modulation of cortical excitability by transcranial direct current stimulation. Nervenarzt 73, 332–335.
Nitsche, M.A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., Henning, S., Tergau, F., Paulus, W., 2003a. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J. Physiol. 553, 293–301.
Nitsche, M.A., Liebetanz, D., Antal, A., Lang, N., Tergau, F., Paulus, W., 2003b. Modulation of cortical excitability by weak direct current stimulation — technical, safety and functional aspects. Suppl. Clin. Neurophysiol. 56, 255–276.
Nitsche, M.A., Nitsche, M.S., Klein, C.C., Tergau, F., Rothwell, J.C., Paulus, W., 2003c. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin. Neurophysiol. 114, 600–604.
Nitsche, M.A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., Tergau, F., 2003d. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. J. Cogn. Neurosci. 15, 619–626.
Nitsche, M.A., Seeber, A., Frommann, K., Klein, C.C., Rochford, C., Nitsche, M.S., Fricke, K., Liebetanz, D., Lang, N., Antal, A., Paulus, W., Tergau, F., 2005. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J. Physiol. 568, 291–303.
Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F., Pascual-Leone, A., 2008. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 1, 206–223.
Ohn, S.H., Park, C.I., Yoo, W.K., Ko, M.H., Choi, K.P., Kim, G.M., Lee, Y.T., Kim, Y.H., 2008. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. NeuroReport 19, 43–47.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
Pae, J.S., Kwon, J.S., Youn, T., Park, H.J., Kim, M.S., Lee, B., Park, K.S., 2003. LORETA imaging of P300 in schizophrenia with individual MRI and 128-channel EEG. Neuroimage 20, 1552–1560.

Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Nitsche, M., Reisinger, E., Padberg, F., 2008. Skin lesions after treatment with transcranial direct current stimulation (tDCS). Brain Stimul. 1, 386–387.
Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Reisinger, E., Baghai, T.C., Mulert, C., Padberg, F., 2009. Transcranial direct current stimulation in a patient with therapy-resistant major depression. World J. Biol. Psychiatry 10, 632–635.
Pascual-Marqui, R.D., 2002. Standardized low-resolution brain electromagnetic tomography sLORETA): technical details. Meth. Find. Exp. Clin. Pharmacol. 24 (Suppl D), 5–12.
Pascual-Marqui, R.D., Michel, C.M., Lehmann, D., 1994. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int. J. Psychophysiol. 18, 49–65.
Pascual-Marqui, R.D., Esslen, M., Kochi, K., Lehmann, D., 2002. Functional imaging with low-resolution brain electromagnetic tomography (LORETA): a review. Meth. Find. Exp. Clin. Pharmacol. 24 (Suppl C), 91–95.
Pizzagalli, D., Pascual-Marqui, R.D., Nitschke, J.B., Oakes, T.R., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Koger, J.V., Benca, R.M., Davidson, R.J., 2001. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. Am. J. Psychiatry 158, 405–415.
Pizzagalli, D.A., Oakes, T.R., Fox, A.S., Chung, M.K., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Benca, R.M., Davidson, R.J., 2004. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol. Psychiatry 9 (325), 393–405.
Polich, J., 2007. Updating P300: an integrative theory of P3a and P3b. Clin. Neurophysiol. 118, 2128–2148.
Poreisz, C., Boros, K., Antal, A., Paulus, W., 2007. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res. Bull. 72, 208–214.
Priori, A., Mameli, F., Cogiamanian, F., Marceglia, S., Tiriticco, M., Mrakic-Sposta, S., Ferrucci, R., Zago, S., Polezzi, D., Sartori, G., 2008. Lie-specific involvement of dorsolateral prefrontal cortex in deception. Cereb. Cortex 18, 451–455.
Purpura, D.P., McMurtry, J.G., 1965. Intracellular activities and evoked potential changes during polarization of motor cortex. J. Neurophysiol. 28, 166–185.
Ramsoy, T.Z., Liptrot, M.G., Skimminge, A., Lund, T.E., Sidaros, K., Christensen, M.S., Baare, W., Paulson, O.B., Jernigan, T.L., 2009. Regional activation of the human medial temporal lobe during intentional encoding of objects and positions. Neuroimage 47, 1863–1872.
Rigonatti, S.P., Boggio, P.S., Myczkowski, M.L., Otta, E., Fiquer, J.T., Ribeiro, R.B., Nitsche, M.A., Pascual-Leone, A., Fregni, F., 2008. Transcranial direct stimulation and fluoxetine for the treatment of depression. Eur. Psychiatry 23, 74–76.
Siapas, A.G., Lubenov, E.V., Wilson, M.A., 2005. Prefrontal phase locking to hippocampal theta oscillations. Neuron 46, 141–151.
Sparing, R., Dafotakis, M., Meister, I.G., Thirugnanasambandam, N., Fink, G.R., 2007. Enhancing language performance with non-invasive brain stimulation-A transcranial direct current stimulation study in healthy humans. Neuropsychologia 46, 261–268.
Speer, A.M., Kimbrell, T.A., Wassermann, E.M., Repella, J.D., Willis, M.W., Herscovitch, P., Post, R.M., 2000. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol. Psychiatry 48, 1133–1141.
Stagg, C.J., Best, J.G., Stephenson, M.C., O'Shea, J., Wylezinska, M., Kincses, Z.T., Morris, P.G., Matthews, P.M., Johansen-Berg, H., 2009. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J. Neurosci. 29, 5202–5206.
Tadini, L., El-Nazer, R., Brunoni, A.R., Williams, J., Carvas, M., Boggio, P., Priori, A., Pascual-Leone, A., Fregni, F., 2010. Cognitive, mood, and electroencephalographic effects of noninvasive cortical stimulation with weak electrical currents. J. ECT. doi:10.1097/YCT.0b013e3181e631a8.
van den Heuvel, M.P., Mandl, R.C., Kahn, R.S., Hulshoff Pol, H.E., 2009. Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. Hum. Brain Mapp. 30, 3127–3141.
Vandermeeren, Y., Jamart, J., Ossemann, M., 2010. Effect of tDCS with an extracephalic reference electrode on cardio-respiratory and autonomic functions. BMC Neurosci. 11, 38.
Vitacco, D., Brandeis, D., Pascual-Marqui, R., Martin, E., 2002. Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. Hum. Brain Mapp. 17, 4–12.
Wacker, J., Dillon, D.G., Pizzagalli, D.A., 2009. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. Neuroimage 46, 327–337.
Wassermann, E.M., Grafman, J., 2005. Recharging cognition with DC brain polarization. Trends Cogn. Sci. 9, 503–505.
Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. J. Pers. Soc. Psychol. 54, 1063–1070.
Wittchen, H.U., Müller, N., 1998. M-CIDI-S. Gesundheitswesen 60, 95–100.
Zumsteg, D., Friedman, A., Wennberg, R.A., Wieser, H.G., 2005a. Source localization of mesial temporal interictal epileptiform discharges: correlation with intracranial foramen ovale electrode recordings. Clin. Neurophysiol. 116, 2810–2818.
Zumsteg, D., Wennberg, R.A., Treyer, V., Buck, A., Wieser, H.G., 2005b. H2(15)O or 13NH3 PET and electromagnetic tomography (LORETA) during partial status epilepticus. Neurology 65, 1657–1660.
Zumsteg, D., Lozano, A.M., Wennberg, R.A., 2006. Depth electrode recorded cerebral responses with deep brain stimulation of the anterior thalamus for epilepsy. Clin. Neurophysiol. 117, 1602–1609.

Supplementary Material – Table

		Baseline			After Real tDCS			After Sham tDCS		
		Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
0-back	Miss rate	↑r=0.40 p=0.38	↓r=-0.02 p=0.96	↑r=0.63 p=0.13	↑r=0.50 p=0.25	↓r=-0.31 p=0.50	↑r=-0.29 p=0.53	↑r=0.58 p=0.18	↑r=0.04 p=0.92	↑r=0.21 p=0.66
	Accuracy	↓r=-0.40 p=0.38	↑r=0.02 p=0.96	↓r=-0.63 p=0.13	↓r=-0.52 p=0.23	↑r=0.35 p=0.45	↓r=-0.05 p=0.92	↓r=-0.57 p=0.19	↓r=-0.04 p=0.93	↓r=-0.22 p=0.63
	Error rate	*No error*	*No error*	*No error*	↑r=0.55 p=0.320	↓r=-0.61 p=0.15	↓r=-0.41 p=0.36	↓r=-0.21 p=0.65	↓r=-0.03 p=0.95	↑r=0.17 p=0.71
	Reaction time	↓r=-0.22 p=0.64	↑r=0.23 p=0.63	↓r=-0.63 p=0.13	↑r=0.49 p=0.26	↓r=-0.32 p=0.49	↓**r=-0.73 p=0.06**$^{\neq}$	↑r=0.62 p=0.14	↑r=0.32 p=0.48	↑r=0.29 p=0.53
1-back	Miss rate	↑r=0.41 p=0.36	↑r=0.036 p=0.94	↑r=0.21 p=0.66	↑**r=0.85 p=0.02***	↑r=0.07 p=0.88	↑**r=0.69 p=0.09**$^{\neq}$	↑r=0.19 p=0.69	↓r=-0.45 p=0.31	↓r=-0.45 p=0.31
	Accuracy	↓r=-0.54 p=0.21	↓r=-0.37 p=0.42	↓r=-0.24 p=0.59	↓**r=-0.84 p=0.019***	↓r=-0.07 p=0.88	↑r=0.39 p=0.39	↓r=-0.26 p=0.57	↑r=0.55 p=0.20	↑r=0.66 p=0.11
	Error rate	↑r=0.51 p=0.24	↑r=0.52 p=0.23	↑r=0.24 p=0.61	↑r=0.46 p=0.30	↓r=-0.38 p=0.40	↓r=-0.55 p=0.21	↑r=0.52 p=0.24	↓r=-0.48 p=0.27	↓r=-0.63 p=0.13
	Reaction time	↑r=0.65 p=0.12	↑r=0.61 p=0.14	↓r=0.15 p=0.76	↑**r=0.75 p=0.06**$^{\neq}$	↑r=0.01 p=0.83	↓r=-0.51 p=0.24	↑r=0.58 p=0.17	↑r=0.01 p=0.98	↓r=-0.12 p=0.80
2-back	Miss rate	↑r=0.16 p=0.73	↓r=-0.34 p=0.46	↓r=-0.10 p=0.83	↓r=-0.66 p=0.10	↓r=-0.58 p=0.18	↓r=-0.44 p=0.33	↑r=0.35 p=0.45	↓r=-0.49 p=0.27	↓r=-0.31 p=0.49
	Accuracy	↓r=-0.044 p=0.93	↑r=0.63 p=0.13	↑r=0.55 p=0.20	↑r=0.57 p=0.18	↑r=0.49 p=0.26	↑r=0.66 p=0.11	↓r=-0.49 p=0.27	↑r=0.31 p=0.5	↑r=0.41 p=0.36
	Error rate	↓r=-0.13 p=0.78	↓r=-0.67 p=0.10	↓**r=-0.78 p=0.039***	↓r=-0.11 p=0.82	↓r=-0.16 p=0.74	↓**r=-0.79 p=0.035***	↑r=0.39 p=0.38	↑r=0.19 p=0.69	↓r=-0.31 p=0.49
	Reaction time	↑r=0.21 p=0.65	↓r=-0.35 p=0.45	↓r=-0.37 p=0.41	↑r=0.39 p=0.38	↓r=-0.35 p=0.45	↓**r=-0.87 p=0.011***	↑**r=0.73 p=0.064**$^{\neq}$	↓r=-0.11 p=0.81	↓r=-0.40 p=0.38

Table S1
Relation between P3 Voltage (μV) and behavioural n-back results (miss rate, accuracy, error rate, reaction time) for the electrodes Fz, Cz and Pz.
* $p < 0.05$, $^{\neq} p < 0.1$, ↑ positive correlation ↓ negative correlation.

2.2 Prefrontal transcranial Direct Current Stimulation (tDCS) modulates resting-state functional connectivity in healthy subjects: a functional magnetic resonance imaging (fMRI) study

Nachdem wir Effekte von präfrontaler tDCS auf das EEG im Ruhezustand feststellen konnten und es Hinweise darauf gibt, dass tDCS einen Einfluss auf die funktionelle Konnektivität hat, wurde eine funktionelle Magnetresonanztomographie-Konnektivitätsstudie (fcfMRI) bei gesunden Probanden durchgeführt. Zu diesem Zeitpunkt gab es noch keine weiteren Studien zu dieser Forschungsfrage. Unsere Ergebnisse deuten darauf hin, dass präfrontale tDCS die funktionelle Konnektivität moduliert. Besonders die Erhöhung der fronto-parietalen Konnektivität weist auf eine Modulation in einem Netzwerk hin, welches als verhaltensrelevant für multiple kognitive Prozesse wie Gedächtnis-, Aufmerksamkeits- und Inhibitationsprozesse angesehen werden kann (Laird et al., 2011).

Behavioral/Systems/Cognitive

Prefrontal Transcranial Direct Current Stimulation Changes Connectivity of Resting-State Networks during fMRI

Daniel Keeser,[1,2]* Thomas Meindl,[2]* Julie Bor,[1,3] Ulrich Palm,[1] Oliver Pogarell,[1] Christoph Mulert,[6] Jerome Brunelin,[3,4,5] Hans-Jürgen Möller,[1] Maximilian Reiser,[2] and Frank Padberg[1]

Departments of [1]Psychiatry and Psychotherapy, and [2]Clinical Radiology, Ludwig-Maximilians University, 80333 Munich, Germany, [3]Université de Lyon, F-69003 Lyon, France, [4]Université de Lyon 1, Lyon, EA4166, CH Le Vinatier, F-69677 Bron, France, [5]Institut Fédératif des Neurosciences de Lyon, Hôpital Neurologique, F-69394 Bron, France, and [6]Department of Psychiatry, University of Hamburg, 20146 Hamburg, Germany

Transcranial direct current stimulation (tDCS) has been proposed for experimental and therapeutic modulation of regional brain function. Specifically, anodal tDCS of the dorsolateral prefrontal cortex (DLPFC) together with cathodal tDCS of the supraorbital region have been associated with improvement of cognition and mood, and have been suggested for the treatment of several neurological and psychiatric disorders. Although modeled mathematically, the distribution, direction, and extent of tDCS-mediated effects on brain physiology are not well understood. The current study investigates whether tDCS of the human prefrontal cortex modulates resting-state network (RSN) connectivity measured by functional magnetic resonance imaging (fMRI). Thirteen healthy subjects underwent real and sham tDCS in random order on separate days. tDCS was applied for 20 min at 2 mA with the anode positioned over the left DLPFC and the cathode over the right supraorbital region. Patterns of resting-state brain connectivity were assessed before and after tDCS with 3 T fMRI, and changes were analyzed for relevant networks related to the stimulation–electrode localizations. At baseline, four RSNs were detected, corresponding to the default mode network (DMN), the left and right frontal-parietal networks (FPNs) and the self-referential network. After real tDCS and compared with sham tDCS, significant changes of regional brain connectivity were found for the DMN and the FPNs both close to the primary stimulation site and in connected brain regions. These findings show that prefrontal tDCS modulates resting-state functional connectivity in distinct functional networks of the human brain.

Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive stimulation technique of the cerebral cortex by means of a weak constant direct current (DC; usually 1–2 mA) applied to the scalp surface. At the primary motor cortex, anodal tDCS induces excitatory effects, whereas cathodal stimulation results in inhibitory effects on motor cortex excitability (Nitsche and Paulus, 2000; Nitsche et al., 2003). Based on early experimental work investigating DC effects on neuronal activity in animal models, it has been hypothesized that tDCS-mediated effects are related to a shift in neuronal resting membrane potential either toward depolarization and increased spontaneous neuronal firing (anodal tDCS) or toward hyperpolarization and decreased firing (cathodal tDCS) (Bindman et al., 1964).

Received Feb. 1, 2011; revised Aug. 2, 2011; accepted Aug. 8, 2011.

Author contributions: T.M., H.-J.M., M.R., and F.P. designed research; D.K., J. Bor, U.P., and O.P. performed research; D.K., T.M., J. Bor, C.M., and J. Brunelin analyzed data; D.K., T.M., and F.P. wrote the paper.

This study was financially supported by Aspect Medical Systems Inc. (Norwood, MA). Neuroconn GmbH (Ilmenau, Germany) has provided DC stimulators for rent. This study is part of the PhD thesis of Daniel Keeser at the Faculty of Medicine of the Ludwig-Maximilians University of Munich (in preparation). Moreover, we gratefully acknowledge F. Esposito for his invaluable advice; and thank M. Hartmann, D. Maxwell, H.J. Engelbregt, and D. Todder for critically reading the manuscript.

*D.K. and T.M. contributed equally to this work.

Correspondence should be addressed to Dr. Frank Padberg, Department of Psychiatry and Psychotherapy, Ludwig-Maximilians University of Munich, D-80336 Munich, Germany. E-mail: padberg@med.uni-muenchen.de.

DOI:10.1523/JNEUROSCI.0542-11.2011

 0270-6474/11/3115284-10$15.00/0

Numerous studies have investigated the effect of prefrontal cortex tDCS in healthy subjects and patients with neurological or psychiatric disorders. Anodal tDCS of the dorsolateral prefrontal cortex (DLPFC) with the cathode placed over the contralateral supraorbital region has been found to improve performance in several cognitive domains, including executive functions, verbal skills, and memory performance in healthy subjects (Iyer et al., 2005; Wassermann and Grafman, 2005; Cerruti and Schlaug, 2009; Sparing et al., 2008; Dockery et al., 2009; Fiori et al., 2011), as well as in patients with Parkinson's disease and stroke (Boggio et al., 2006; Jo et al., 2009). Promising pilot data suggest a positive therapeutic effect in patients with major depression (Fregni et al., 2006; Boggio et al., 2008; Rigonatti et al., 2008; Ferrucci et al., 2009). Moreover, prefrontal tDCS could influence the emotional-affective domain of the self (Boggio et al., 2009; Karim et al., 2010; Mameli et al., 2010).

Although these studies are encouraging from a clinical point of view, the distribution, direction, and extent of tDCS-mediated effects on brain physiology are not well understood. However, specific hypotheses regarding the neurophysiological action of tDCS seem crucial to further tailor tDCS for experimental and therapeutic applications. Neuroimaging studies using positron emission tomography (PET) (Lang et al., 2005) or functional magnetic resonance imaging (fMRI) have shown widespread (Kwon et al., 2008; Stagg et al., 2009) and subtle (Baudewig et al., 2001) cortical and subcortical

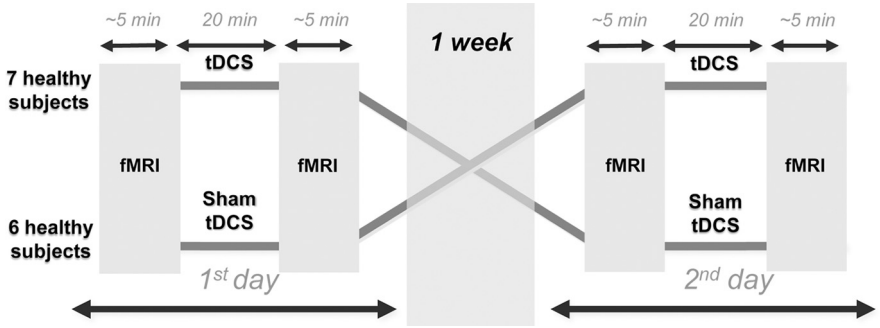

Figure 1. Experimental protocol. Real and sham tDCS conditions were applied in random order after baseline fMRI scans within a double-blind, crossover design.

changes in regional brain activity following anodal tDCS of the primary motor cortex.

To further investigate the effects of prefrontal tDCS on functional connectivity, we conducted resting-state fMRI measurements, which were subsequently analyzed using independent component analysis (ICA). During, the last decade, an emerging number of resting-state fMRI studies have demonstrated the existence of coherent fluctuations in functionally related regions of the brain (Greicius et al., 2003; Damoiseaux et al., 2006; De Luca et al., 2006; Biswal et al., 2010). We hypothesized that changes of functional connectivity would be detectable in resting-state networks (RSNs) comprising regions within the prefrontal cortex [i.e., the default mode network (DMN), the frontal-parietal network (FPN), and the self-referential network (SRN)], as well as in areas below or close to the stimulation electrodes.

Materials and Methods

Subjects. After giving their written informed consent, 13 healthy male volunteers (mean age: 27.4 years; age range: 23–32 years) participated in this double-blind, placebo-controlled, and randomized study. All subjects were right-handed (Edinburgh Handedness Inventory) (Oldfield, 1971) and went through a semistructured interview to exclude a history of neurological and psychiatric diseases and the intake of medication affecting the CNS. The study was approved by the local ethics committee (Department of Psychiatry and Psychotherapy, Ludwig Maximilians University Munich, Munich, Germany).

Experimental design. The study was conducted in a double-blind and placebo-controlled design to guarantee that neither subjects nor researchers were aware of the stimulation condition. The blinding was reversed after all steps of the procedure were completed. All subjects underwent two tDCS sessions (real and sham tDCS) in random order and counterbalanced across subjects on 2 separate days with a 1 week interval between both stimulations (Fig. 1). All tDCS-fMRI sessions were scheduled between 4:00 and 8:00 P.M. The first resting-state fMRI scan was conducted before each tDCS procedure (baseline1′, baseline2′), and another scan was conducted after each tDCS procedure (real tDCS or sham tDCS). The second scan was started immediately after stimulation, and not later than 5 min after stimulation. The time delay between the end of stimulation and the start of the fMRI scan was recorded.

Transcranial direct current stimulation. Bipolar tDCS was administered using two saline-soaked surface sponge electrodes (area = 7×5 cm^2) and delivered by an Eldith DC stimulator (neuroConn). The anode was placed above F3 (according to the EEG international 10–20 system) corresponding to the left DLPFC, and the cathode was positioned above the contralateral supraorbital region, at least 5 cm from the anode (Miranda et al., 2006). DC stimulation was delivered for a duration of 20 min at 2 mA intensity (15 s ramp in and 15 s ramp out).

For sham tDCS, the Eldith DC stimulator has a built-in placebo mode, which is activated by a code number and includes ramp periods at the beginning and the end of sham stimulation to mimic the somatosensory artifact of real tDCS. Thus, placebo tDCS could be identified neither by the operator who administered tDCS nor by the subjects participating in the trial (Gandiga et al., 2006).

The impedance was controlled by the device throughout each tDCS session, ranging <10 kΩ and limited by the voltage at <26 V. An excess of limits (e.g., an increase of impedance by drying up or chute of the electrodes) would have led to an automatic termination of stimulation.

Functional MRI acquisition. For resting-state data acquisition, subjects were instructed to keep their eyes closed without falling asleep and try to think of nothing in particular.

Each subject was scanned using a 3.0 T magnetom (VERIO, Siemens). For functional imaging, an EPI sequence with the following parameters was used: repetition time (TR), 3000 ms; echo time (TE), 30 ms; flip angle (FA), 90°; spatial resolution, $3 \times 3 \times 4$ mm^3; imaging matrix, 64×64; field-of-view (FoV), 192×192 mm^2; number of slices, 28; number of volumes, 120. Functional images were acquired in axial orientation. For anatomical reference, a high-resolution MPRAGE was performed with the following specifications: FoV, 256×240 mm^2; spatial resolution, $1 \times 1 \times 1$ mm^3; TR, 14 ms; TE, 7.61 ms; FA, 20°; number of slices, 160.

Functional MRI analysis. All image data analyses were performed using FSL 4.16 (http://www.fmrib.ox.ac.uk/fsl/index.html). Individual high-resolution T1-weightened images were processed using AFNI (Analyses of Functional Images, http://afni.nimh.nih.gov/afni). The first five functional scans of each session were discarded to account for T1 effects.

We used the FEAT (FMRI Expert Analysis Tool) analysis tool box, version 5.98 (Smith et al., 2004) for the preprocessing of fMRI resting-state data. Head motion correction was done using MCFLIRT [Motion Correction using the FMRIB (Oxford Centre for Functional MRI of the Brain) Linear Image Registration Tool] (Jenkinson et al., 2002). The skull was removed using BET (Brain Extraction Tool) (Smith, 2002) followed by spatial smoothing using a 5 mm FWHM Gaussian kernel with high-pass temporal filtering (Gaussian-weighted, least-squares, straight-line fitting with $\sigma = 50$ s). Registration to the individual high-resolution T1-weighted images, and afterward to the MNI-152 standard space template, was performed using FLIRT, version 5.5 (Jenkinson et al., 2002). The preprocessed four-dimensional (4D) datasets were resampled to 2 mm isotropic voxels in the following group analyses.

Independent component analysis. ICA was performed on all resting-state runs using the MELODIC (Multivariate Exploratory Linear Optimized Decomposition) routine, version 3.10, implemented in FSL (Beckmann and Smith, 2004). Decomposition into different functional networks was performed automatically by a dimensionality estimation of the MELODIC 3.10 tool.

Since spontaneous resting-state connectivity measured by BOLD fMRI may comprise ultraslow frequencies (Greicius et al., 2003; Fox et al., 2005; Damoiseaux et al., 2006; Vincent et al., 2007; Boly et al., 2008; Horovitz et al., 2009; Miller et al., 2009), only independent components with signals in the range of 0.01–0.1 were included. Higher-frequency signals with respiratory (0.1–0.5 Hz) or cardiovascular (0.6–1.2 Hz) origin were excluded (Cordes et al., 2000, 2001; van de Ven et al., 2004; De Martino et al., 2007).

Resting-state datasets of all subjects and experimental conditions (baseline1, baseline2, after real tDCS and after sham tDCS) were concatenated in time to create a single 4D dataset. After ICA decomposition of these datasets, we chose four resting-state networks, which are known to involve brain regions within the prefrontal cortex close to tDCS electrode sites: the DMN, the left FPN, the right FPN and the SRN. An average z-score of $2.3 < z < 10$ was defined as the threshold for the resulting statistical group maps. The alternative was that the resulting statistical group maps were thresholded at $z < 2.3$.

Group-level analyses. A validated dual-regression approach was used (Filippini et al., 2009; Biswal et al., 2010; Zuo et al., 2010). The dual-

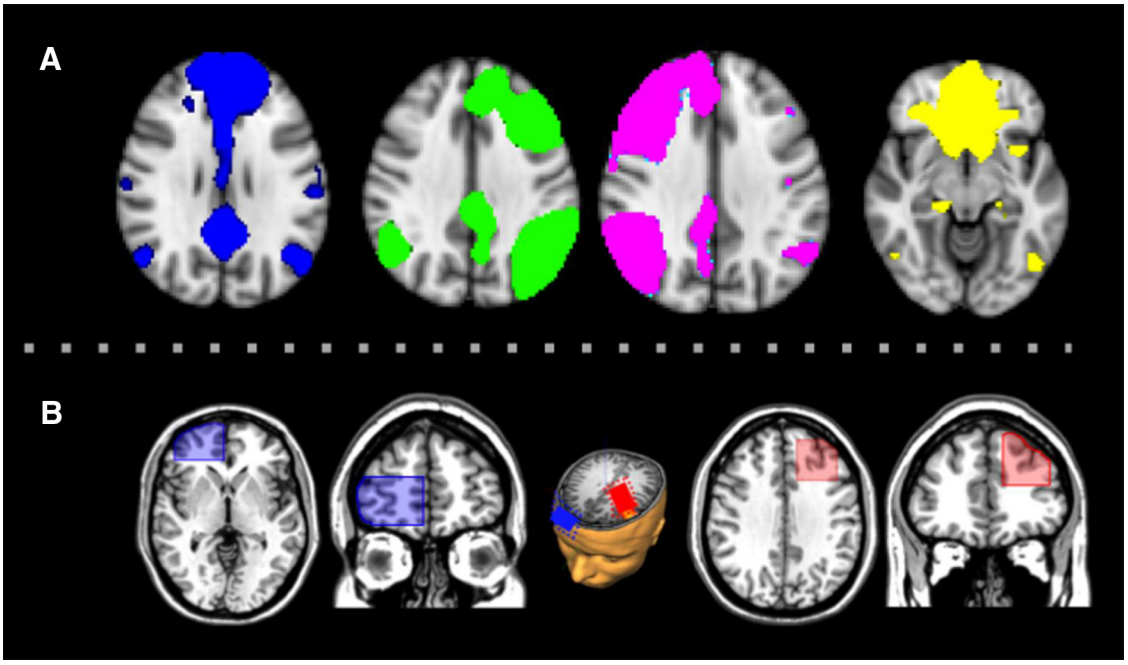

Figure 2. Study-specific masks. ***A***, RSN masks were created using the group average ICA of all subjects including all conditions. ***B***, Electrode position masks were defined according to EEG positions F3 (anode) and Fp2 (cathode) of the international 10–20 electrode system. A representative T1 image projected on the MNI-T1 Colin 1 mm template (Holmes et al., 1998) from one of the subjects illustrates the localization of the stimulation electrodes.

regression approach summons several processing steps starting with a temporal concatenation of all time series into a single 4D time series file. Another process includes the registration of all individual time series with regard to the estimated group RSNs using spatial regression against the individual datasets. Additionally, the temporal dynamics at the subject level were regressed against the primary data.

In a hypothesis-driven approach, we analyzed (1) the effects restricted to the RSN templates to specifically measure the effects of tDCS on RSN connectivity, and (2) the effects below both stimulation electrodes to measure local effects at primary stimulation sites. The respective masks are shown in Figure 2. In an additional exploratory approach, the four RSNs were analyzed against fluctuations in the entire brain.

The chosen RSNs were thresholded at $p < 0.01$ ($z = 2.32$). The areas below the tDCS electrodes were defined as regions of interest (ROIs) using EEG positions F3 (anode) and Fp2 (cathode) of the international 10–20 electrode system. Conversions from these coordinates to MNI coordinates were drawn from the center of the stimulation electrodes (MNI coordinates for F3: $x = -34$, $y = 26$, $z = 44$; for Fp2: $x = 29$, $y = 84$, $z = -10$) according to the 10–20 electrode system on the closest MNI cortical standard space using the Münster T2T-Converter (O. Steinsträter, J. Sommer, M. Deppe, S. Knecht, unpublished observations; http://wwwneuro03.uni-muenster.de/ger/t2tconv/) and then converted to a binary form. The electrode ROIs were positioned for each subject separately with a cube width of 35 mm horizontal (anode) or vertical (cathode) using MANGO (Multi-Image Analysis GUI) software (http://ric.uthscsa.edu/mango/mango.html). Areas outside the cortex were rejected individually (Fig. 2*B*).

Masks of the RSNs and the theoretically chosen area below the anode and the cathode electrodes were created for each subject and all four conditions separately. The average MNI coordinates for F3 were comparable to that used by Miranda et al. (2006), with the difference that we used an electrode size of 35 cm^2 and not 25 cm^2.

The resulting seed time courses for each region and subject were generated by averaging the signal within the ROIs. This was done for each time course and for all conditions. To include only gray matter within the ROIs, we removed possible nuisance confounders: six different motion parameters, white matter, the CSF signals, and the global signal based on the approach of Biswal et al. (2010).

Each subject's maps of the four RSNs were combined to a single 4D dataset for each network, and dual regression was performed for each of the 4 RSNs separately.

The following contrasts were calculated: (real > baseline1) > (sham > baseline2); (real > baseline1) < (sham > baseline2); real > baseline1; real < baseline1; sham > baseline2; sham < baseline2; and baseline1 > baseline2. We applied a statistical threshold with family-wise error rate (threshold-free cluster enhancement) corrected for multiple comparisons (Smith and Nichols, 2009) of p values <0.05 with a cluster extent of >20 voxels. We report only the contrasts (real > baseline1) > (sham > baseline2), (real > baseline1) < (sham > baseline2), real > baseline1, real < baseline1 for the whole-brain analysis approach descriptively (see Table 3).

The dual-regression analysis produces z-score maps representing connectivity within the four RSNs. We used Randomize 2.6 (permutation-based nonparametric inference) to determine the voxelwise nonparametric statistical contrasts (with 5000 permutations) (Nichols and Holmes, 2002) between the conditions for the four selected networks. Due to the exploratory character of the second analysis, effects were considered significant at a level of $p_{\text{uncorrected}} < 0.001$ with a cluster extent of >20 voxels.

Results

Overall, neither side effects nor any relevant discomfort were observed during the experiment, and tDCS was generally well tolerated. Moreover, subjects were not able to guess whether they had received real or sham tDCS.

Detection of resting-state networks

Four RSNs relevant for higher cognition were identified using group clustering of subjects resting-state fMRI data before stimulation: the first network (RSN1) was consistent with the DMN and comprised the posterior cingulate cortex/precuneus [Brodmann's area (BA) 23/31], the middle/superior temporal gyrus bilaterally (BA 31/39), the superior frontal gyrus bilaterally (BA 8/9), and the ventromedial prefrontal cortex bilaterally (BA 10/11). A second network (RSN2) was identified as the left FPN,

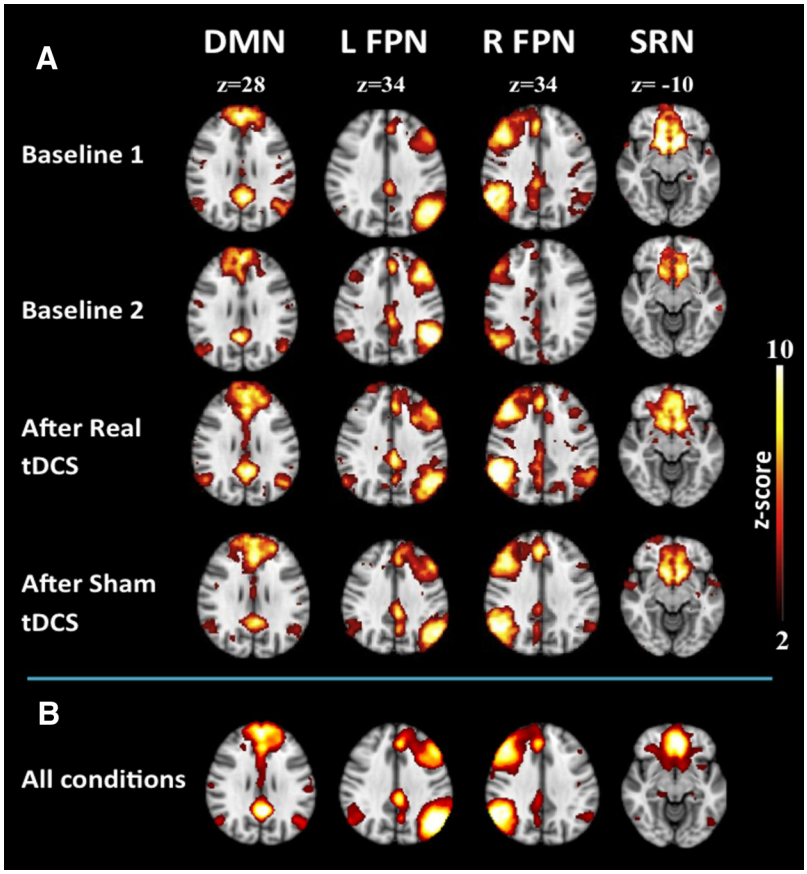

Figure 3. Group analysis of RSN time series. Group analysis of resting-state time series of the 13 subjects revealed four resting-state networks. ***A***, The DMN, left FPN (L FPN), right FPN (R FPN), and SRN are shown before real tDCS, after real tDCS, and after sham tDCS, respectively. ***B***, Group ICA RSNs derived from resting-state scans of all individuals during all conditions. Group analyses of RSN time series are shown for the conditions baseline1, baseline2, after real tDCS, and after sham tDCS.

consisting of the left middle (BA 8/9/10/46) and the left superior parietal lobule (BA 7/40). A third network (RSN3) comprised the right superior frontal gyrus/middle frontal gyrus (BA 8/9/10/46) and the right inferior parietal lobule (BA 7/40) (right FPN). The fourth network (RSN4) included the anterior cingulate (BA 24/32) and the subgenual gyrus (BA 25), and was consistent with the SRN.

Activation patterns of the four different functional networks are shown in Figure 3.

Effects of tDCS on functional connectivity

Within the ROI templates for different RSNs, neither a significant difference between baseline scans nor any significant effect of sham tDCS compared with baseline was observed. Significant effects were identified for real > baseline1 and (real > baseline1) > (sham > baseline2) comparisons within RSN1 (DMN), RSN2 (left FPN), and RSN3 (right FPN), whereas no significant differences were found for RSN 4 (SRN). Detailed results are shown in Figure 4 and Table 1.

When exploring the local effects of tDCS that were dependent on the electrode positions, an increased coactivation outside RSN 1 (DMN), but within the anode ROI, was observed in the left middle frontal gyrus ($x = -20$, $y = 22$, $z = 56$; BA 6; 32 voxels). Increased coactivations were also observed outside the FPN masks in the left superior frontal gyrus (outside the left FPN mask: $x = -30$, $y = 52$, $z = 28$; BA 9; 25 voxels) and the left middle frontal gyrus (outside the right FPN mask: $x = -38$, $y = 48$, $z = 18$; BA 10; 31 voxels).

In addition to the hypothesis-driven ROI analyses, whole-brain dual-regression analysis showed significant effects for the comparison (real > baseline1) > (sham > baseline2) in all four RSNs at an uncorrected $p < 0.001$ (cluster size, >20 voxels). These findings are presented in Table 2 and Figure 5. The results for the comparison real tDCS > baseline1 are shown in Table 3.

Discussion

Combining prefrontal tDCS and resting-state fMRI, this study shows that prefrontal tDCS modulates large-scale patterns of resting-state connectivity in the human brain by inducing changes of functional connectivity close to anode and cathode stimulation sites, but also in distant brain regions. These effects were detectable in three resting-state networks (i.e., the DMN as well as the left and right FPN), involving brain regions of higher cognitive functions (Raichle and Gusnard, 2002; Greicius et al., 2003; Damoiseaux et al., 2006; Laufs, 2008; van den Heuvel et al., 2009). Moreover, resting-state fMRI revealed increased coactivations between different frontal brain regions close to or between both tDCS electrodes.

Effects of tDCS on RSNs

Our results suggest that prefrontal tDCS influences coactivation in frontal parts of the DMN, parts of the left frontal-parietal network and the right posterior cingulated cortex (PCC), as well as parts of the right frontal-parietal network. The DMN is thought to reflect an intrinsic state associated with alertness and self-related processes, whereas goal-directed extrinsic cognitive tasks suspend this network (Gusnard et al., 2001; Raichle et al., 2001). The neuronal basis of the DMN has been established using electrocorticographic recordings (He et al., 2008; Miller et al., 2009), and highly reproducible multicenter consistency has been shown for the DMN (Biswal et al., 2010). The DMN has been hypothesized to be involved in cognitive functions associated with intrinsic processing and external inputs (Hampson et al., 2006; Schilbach et al., 2008; Wirth et al., 2011). Although deactivation of DMN components has been reported, some studies show the opposite—a strengthening of DMN components, accompanied by improved working memory (Hampson et al., 2006) or semantic memory performance (Wirth et al., 2011).

Analysis of the left FPN revealed increased coactivations between regions within the frontal lobe, the parietal lobule, and the posterior cingulate gyrus. These frontoparietal coactivations may be localized in well known projections between the DLPFC, the cingulate cortex, and the parietal lobe (Hagmann et al., 2008; van den Heuvel et al., 2008; Bohland et al., 2009; Greicius et al., 2009). Therefore, it could be hypothesized that frontal tDCS increases connectivity within these pathways, which are also part of the

so-called attention network (Laufs et al., 2003; Greicius and Menon, 2004; Fox et al., 2005; Fransson, 2005; van de Ven et al., 2008). Functionally, an increased coactivation of frontal and parietal regions has been related to top-down modulation of attention and working memory (Corbetta and Shulman, 2002). Several studies show an increased activation of left or right frontal-parietal components during cognitive engagement and correct task performance (D'Esposito et al., 1995; Braver et al., 1997; He et al., 2007; Kelly et al., 2008; Volle et al., 2008). The left frontal-parietal network appears to be particularly essential for cognitive functioning as shown by lesion studies (Turken et al., 2008), and increased connectivity within this network has been demonstrated after cognitive training (Lewis et al., 2009; Mazoyer et al., 2009).

Since tDCS led to increased coactivation within parts of the DMN and FPN bilaterally, we hypothesize that tDCS may enhance the state of alertness and therefore impact alertness-dependent cognitive functions. So far, there is growing evidence that the integrity and strength of spontaneous functional connectivity in several networks are of behavioral and cognitive relevance (Massimini et al., 2005; Hampson et al., 2006; He et al., 2007; Schacter et al., 2007; Kelly et al., 2008; Schilbach et al., 2008; Lewis et al., 2009; Ferrarelli et al., 2010; Wirth et al., 2011). Thus, our findings may explain why a wide range of cognitive domains has already been successfully modulated by prefrontal tDCS (Wassermann and Grafman, 2005; Sparing et al., 2008; Cerruti and Schlaug, 2009; Dockery et al., 2009; Elmer et al., 2009; Fertonani et al., 2010; Hecht et al., 2010; Ambrus et al., 2011; Fiori et al., 2011). Within this range of cognitive domains, we have recently shown that prefrontal tDCS using similar stimulation parameters as in the current study, led to an improvement of working memory performance (*n*-back) associated with changes in EEG activity patterns (Keeser et al., 2011).

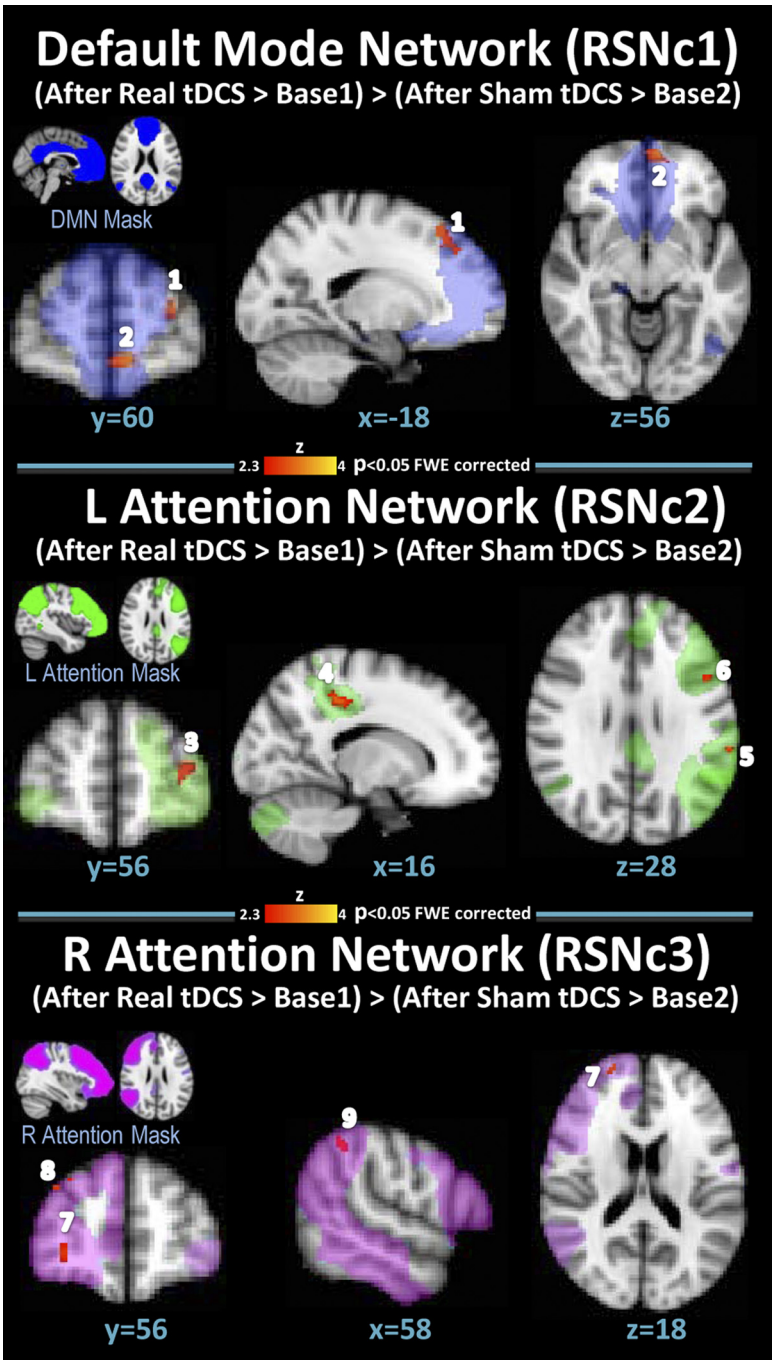

Figure 4. Effects of tDCS on connectivity. Connectivity differences within the RSNs (RSNc 1–3) for the contrasts (after real tDCS > baseline1) > (after sham tDCS > baseline2). Results are cluster corrected for familywise errors ($p < 0.05$). Resting-state network contrast (RSNc) 1 corresponds to the contrast in the DMN, RSNc 2 corresponds to the contrast in the left FPN, and RSNc 3 corresponds to the contrast in the right FPN (radiological convention). Numbers correspond to the clusters presented in Table 1.

Effects of tDCS in models and imaging studies

To predict the distribution of the electric field induced by tDCS in the brain, various electrode positions have been mathematically modeled (Miranda et al., 2006, 2009; Wagner et al., 2007). Using a standard spherical head model together with different bipolar electrode montages at 2 mA stimulation intensity (electrode size 25 cm^2), cortical current densities of ~0.01 mA/cm^2 were calculated (Miranda et al., 2006). However, Wagner et al. (2007) found current density maxima between 0.77 and 2 mA/cm^2 for different electrode montage using 1 mA tDCS on a realistic MRI-derived finite-element model. Thus, previous models resulted in a considerable range of assumed induced peak current densities and showed a nonfocal electric field close to the electrode positions (Miranda et al., 2006; Wagner et al., 2007). In addition to analyzing tDCS effects on resting-state networks, we therefore also applied electrode-specific masks and detected stimulation effects localized close to the cathode, but outside the RSNs. However, the functional relevance of these effects within other distinct networks remains to be clarified. The same is true for the multiple effects in more distant regions revealed by an exploratory whole-brain analysis (uncorrected $p < 0.001$; cluster size, >20 voxels). We present also these data for further com-

Table 1. Significant differences within the RSN-based masks

Contrast/network	Cluster	Brain area	Brodmann's area	Number of voxels	MNI coordinates		
					x	*y*	*z*
(Real > baseline1) > (sham > baseline2), $p < 0.05$ FWE corrected							
RSNc1/default mode	1	L superior frontal gyrus	6/8	81	−22	32	44
	2	L superior frontal gyrus/L anterior cingulate	10/32	62	−6	54	−8
RSNc2/left frontal-parietal	3	L superior frontal gyrus	10	91	−30	56	8
	4	R posterior cingulate gyrus	31	85	16	−26	40
	5	L inferior parietal lobule	40	56	−62	−34	30
	6	L inferior frontal gyrus	9/45	49	−52	14	28
RSNc3/right frontal-parietal	7	R superior frontal gyrus	10	189	28	56	−2
	8	R middle frontal gyrus/R superior frontal gyrus	8/9	103	34	46	36
	9	R inferior parietal lobule	40	42	58	−48	48
Real tDCS > Baseline 1, $p < 0.05$ FWE corrected							
RSNc1/default mode	1	L superior frontal gyrus	8	104	−22	36	46
	2	L medial frontal gyrus/L anterior cingulate	10/32	61	−6	62	−8
RSNc2/left frontal-parietal	3	L inferior frontal gyrus/L middle frontal gyrus	10	95	−40	42	8
	4	L middle frontal gyrus	8	82	−24	30	40
	5	R posterior cingulate	31	49	18	−26	40
	6	L inferior parietal lobule	40	33	−54	−36	44
RSNc3/right	7	R medial frontal gyrus	10	139	20	52	2
	8	R superior frontal gyrus	9	63	28	60	28
	9	R superior parietal lobule	7	54	44	−54	58

Results are cluster corrected for familywise errors ($p < 0.05$) with a cluster size of >20 voxels. Significant clusters are shown for the contrast (real tDCS > baseline1) > (sham > baseline 2) and real tDCS > baseline1 for each of the four networks. Resting-state network contrast (RSNc) 1 corresponds to the contrast of the DMN, RSNc 2 corresponds to the contrast of the left FPN, and RSNc 3 corresponds to the contrast on the right FPN. Results are cluster corrected for familywise errors ($p < 0.05$) with a cluster size of >20 voxels. Numbers correspond to clusters shown in Figure 4.

parison with the results of future studies, but withhold a detailed discussion as these data may contain a considerable number of false-positive results.

To our knowledge, there has only been one functional neuroimaging study published so far focusing on prefrontal tDCS. Merzagora et al. (2010) used functional near-infrared spectroscopy (fNIRS) for investigating the effects of bilateral prefrontal tDCS (1 mA for 10 ms; anode, lateral to Fp1; cathode, lateral to Fp2). They observed a local increase of the concentration of oxyhemoglobin, relatively focal and close to the anode. Our results corroborate and extend this finding by demonstrating tDCS-specific effects on different RSNs, where fNIRS is methodologically limited. However, the majority of previous combined tDCS and functional neuroimaging studies have focused on motor cortex stimulation, also including motor activation paradigms. Most studies found fMRI signal changes close to the stimulation site and in distant regions (Kwon et al., 2008; Jang et al., 2009; Stagg et al., 2009). Lang et al. (2005) used $H_2{}^{15}O$ PET and observed an increased regional cerebral blood flow (rCBF) in widespread cortical and subcortical areas that reached the magnitude of effects of finger movement on rCBF in motor areas and were stable for ~50 min. To further elucidate the network-specific effects of motor cortex tDCS, Polanía et al. (2011) used resting-state fMRI combined with a graph theory approach instead of ICA. They found a decrease in the average number of direct functional connections from the left somatomotor cortex (SM) to topologically distant gray matter regions accompanied by an increase in functional connectivity between SM and the left premotor, motor, and left parietal cortex. In addition, nodal functional connectivity increased in the left PCC and the right DLPFC. Thus, these results suggest a network-specific enhancement of connectivity following motor cortex tDCS and parallel our findings for prefrontal tDCS. Future studies are needed to differentiate these effects in terms of their functional relevance.

Limitations

One limiting factor of the current study is that small sample size may have reduced statistical power. Another factor limiting the interpretation of our findings is the principle difficulty in separating the effects of anodal versus cathodal stimulation for tDCS. Even in experimental designs where different electrode positions are compared, each combination of anode-cathode positions can be regarded as a different bipolar tDCS modality. Also, physical models show that the electric field generated by tDCS is probably distributed throughout the brain (Wagner et al., 2007; Oostendorp et al., 2008; Miranda et al., 2009; Sadleir et al., 2010; Suh et al., 2010). Thus, our findings may just be valid for the specific set of parameters and electrode positions applied in the current study.

A third limitation of our study may be that we did not include a behavioral task to probe the functional relevance of our findings. Further studies are necessary to clarify this issue, and thus the relation between RSN connectivity and cognitive functions discussed above may be regarded as speculative.

Conclusion

In conclusion, our results support the hypothesis that prefrontal tDCS alters the level of neural excitability. We propose that the findings of an augmented connectivity within different RSNs after prefrontal tDCS reflect increased resources and a higher readiness to facilitate cognitive performance. Indeed, there is an increasing body of evidence that prefrontal tDCS acts on different cognitive domains and is clinically effective in several neuropsychiatric disorders. Therefore, resting-state fMRI could become a valuable tool to explore the effects of tDCS on these disorders and may help to tailor the tDCS procedure to individual needs. However, additional studies are necessary to replicate our findings and further specify their relationship to short- and long-term neurocognitive functioning in healthy and patient groups.

References

Ambrus GG, Zimmer M, Kincses ZT, Harza I, Kovács G, Paulus W, Antal A (2011) The enhancement of cortical excitability over the DLPFC before and during training impairs categorization in the prototype distortion task. Neuropsychologia 49:1974–1980.

Baudewig J, Nitsche MA, Paulus W, Frahm J (2001) Regional modulation of

Table 2. Exploratory tDCS effects on RSNs: significant clusters for the contrast (real tDCS > baseline1) > (sham > baseline 2) and (real tDCS > baseline1) < (sham > baseline2) for each of the four networks

Contrast/network	Cluster	Brain area	Brodmann's area	Number of voxels	MNI coordinates		
					x	*y*	*z*
(Real tDCS > baseline 1) > (sham tDCS > baseline2)							
RSNc1/default mode	1	R inferior parietal lobule	40	277	64	−28	44
	1	Postcentral gyrus	3				
	x	R middle frontal gyrus	11	84	28	26	−24
	2	R anterior cingulate	32	77	4	48	−12
	3	L superior frontal gyrus	8	61	−32	26	48
	4	R superior frontal gyrus	8	54	6	50	42
	5	L precuneus/L posterior	7/31	52	−2	−60	38
	6	R middle frontal gyrus	8	41	50	14	42
	7	L middle frontal gyrus	8	40	−48	20	40
	8	L superior frontal gyrus	9	33	−18	52	28
	9	R superior frontal gyrus	8	27	26	40	46
	10	R superior frontal gyrus	8	25	38	32	48
(Real tDCS > baseline1) < (sham tDCS > baseline2)	11	Posterior cingulate	23	114	0	−54	20
	x	L superior temporal gyrus	21	105	−40	−6	−36
	12	L superior frontal gyrus	6	85	−24	26	58
	13	R superior frontal gyrus	6	68	20	20	54
	14	L middle frontal gyrus	6	52	−34	10	60
	15	Brainstem		38	0	−20	−14
RSNc2/left frontal-parietal	1	L inferior frontal gyrus	46/10	206	−42	48	0
	2	L parahippocampal gyrus	30	163	−12	−40	−2
	3	L posterior cingulate	29	162	−12	−44	10
	4	L brainstem		159	−2	−12	−12
	x	R posterior cingulate gyrus	31	158	6	−30	38
	5	R middle frontal gyrus	10	52	40	42	4
	6	R middle frontal gyrus	8	37	38	44	36
	7	L inferior frontal gyrus	44	32	−50	18	10
	8	R inferior parietal lobule	40	31	54	−54	48
	9	R precentral gyrus	44	24	56	16	4
RSNc3/right frontal-parietal	1	R middle frontal gyrus[a]	8/9	444	38	44	36
	2	L middle frontal gyrus	9	327	−44	38	34
	3	R superior parietal lobule	7	191	44	−60	58
	4	R precentral gyrus	44	184	56	12	4
	5	R middle frontal gyrus	10	96	42	44	8
	6	R middle frontal gyrus	9/10	75	38	48	24
	7	R superior frontal gyrus[a]	10	57	16	68	8
	8	R inferior frontal gyrus	11	53	28	26	−24
	9	R superior frontal gyrus	9	27	26	60	26
RSNc4/self-referential	1	L hippocampus/L parahippocampal gyrus	19	228	−30	−48	−4
	2	R hippocampus/R parahippocampal gyrus	19	218	36	−42	−4
	3	L cerebellum culmen		217	−12	−32	−20
	4	L uncus	28	186	−28	4	−28
	5	L brainstem/thalamus		117	−2	−6	−4
	6	L superior temporal gyrus		28	−40	14	−22

Resting-state network contrast (RSNc) 1 corresponds to the contrast on the DMN, RSNc 2 to the contrast on the left FPN and RSNc 3 to the contrast on the right FPN, RSNc 4 corresponds to the contrast of the self referential network. Results are based on a whole brain dual regression approach and presented uncorrected with a $p < 0.001$ (cluster size >20 voxels). Numbers correspond to clusters in Figure 5. *x* = Clusters are not shown in Figure 5.

[a]Connected within one cluster.

BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. Magn Reson Med 45:196–201.

Beckmann CF, Smith SM (2004) Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans Med Imaging 23:137–152.

Bindman LJ, Lippold OC, Redfearn JW (1964) The Action of Brief Polarizing Currents on the Cerebral Cortex of the Rat (1) During Current Flow and (2) in the Production of Long-Lasting after-Effects. J Physiol 172:369–382.

Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, Beckmann CF, Adelstein JS, Buckner RL, Colcombe S, Dogonowski AM, Ernst M, Fair D, Hampson M, Hoptman MJ, Hyde JS, Kiviniemi VJ, Kotter R, Li SJ, Lin CP, et al. (2010) Toward discovery science of human brain function. Proc Natl Acad Sci U S A 107:4734–4739.

Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, Fregni F (2006) Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci 249:31–38.

Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, Fregni F (2008) A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol 11:249–254.

Boggio PS, Zaghi S, Fregni F (2009) Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia 47:212–217.

Bohland JW, Wu C, Barbas H, Bokil H, Bota M, Breiter HC, Cline HT, Doyle JC, Freed PJ, Greenspan RJ, Haber SN, Hawrylycz M, Herrera DG, Hilgetag CC, Huang ZJ, Jones A, Jones EG, Karten HJ, Kleinfeld D, Kötter R, et al. (2009) A proposal for a coordinated effort for the determination of brainwide neuroanatomical connectivity in model organisms at a mesoscopic scale. PLoS Comput Biol 5:e1000334.

Boly M, Phillips C, Balteau E, Schnakers C, Degueldre C, Moonen G, Luxen A, Peigneux P, Faymonville ME, Maquet P, Laureys S (2008) Consciousness and cerebral baseline activity fluctuations. Hum Brain Mapp 29:868–874.

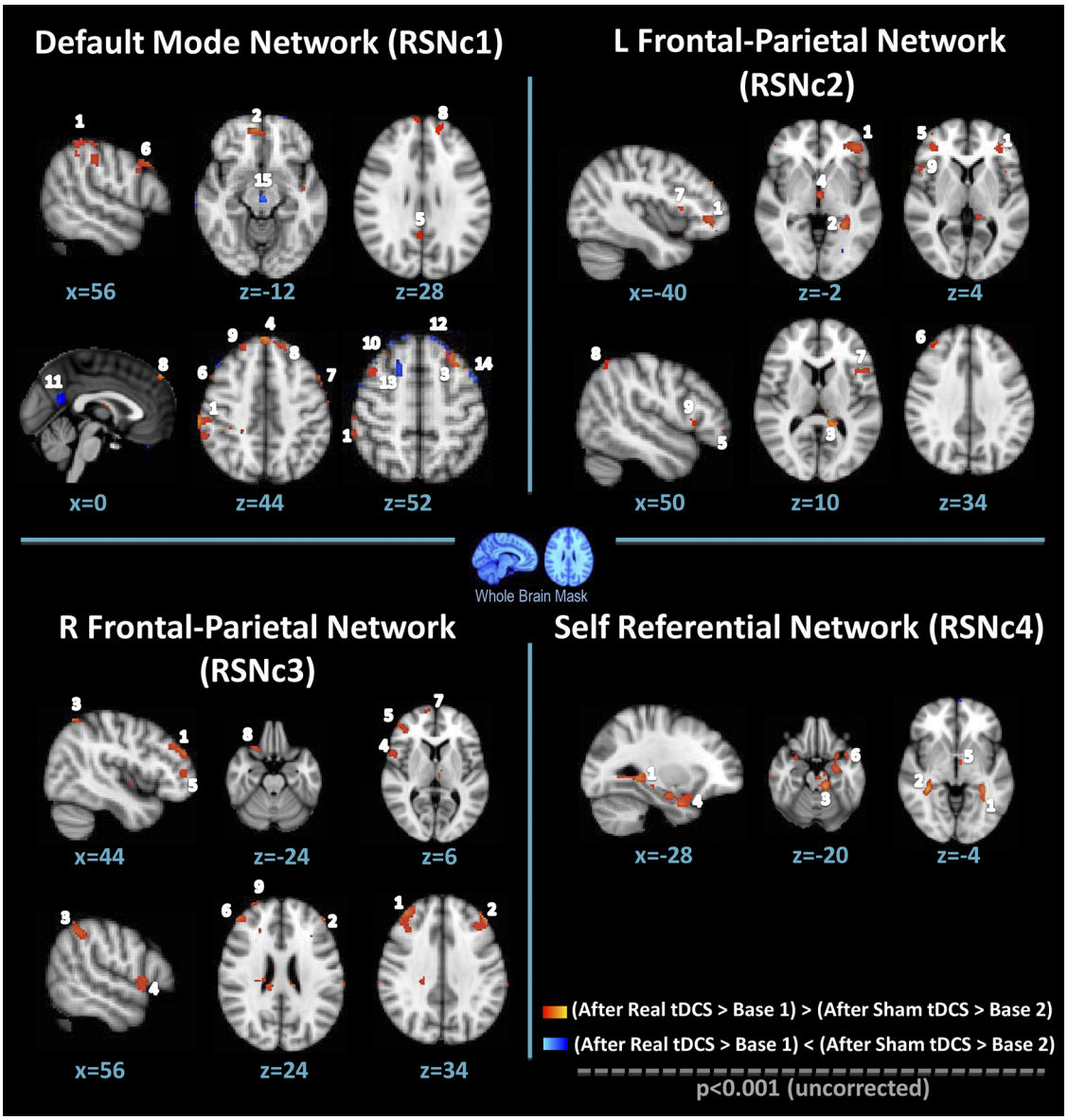

Figure 5. Exploratory analysis of whole-brain tDCS effects. RSN contrasts resulting from the contrast baseline1 > baseline2, real tDCS > baseline12, sham tDCS > baseline12, (after real > before real) > (after sham > before sham), and inverse contrasts for each of the four networks detected after stimulation [resting-state network contrast (RSNc) 1 corresponds to the contrast on the DMN, RSNc 2 to the contrast on the left FPN, RSNc 3 to the contrast on the right FPN, and RSNc4 to the contrast of the SRN]. Numbers correspond to the clusters presented in Table 2. Red color scales represent functional correlation for the contrast (after real tDCS > baseline1) > (after sham tDCS > baseline2), and blue color represents functional correlation for the contrast after real tDCS > baseline1 < (after sham tDCS > baseline2). Radiological convention: $p < 0.001$ (uncorrected); cluster size, >20 voxels.

Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC (1997) A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5:49–62.

Cerruti C, Schlaug G (2009) Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. J Cogn Neurosci 21:1980–1987.

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215.

Cordes D, Haughton VM, Arfanakis K, Wendt GJ, Turski PA, Moritz CH, Quigley MA, Meyerand ME (2000) Mapping functionally related regions of brain with functional connectivity MR imaging. AJNR Am J Neuroradiol 21:1636–1644.

Cordes D, Haughton VM, Arfanakis K, Carew JD, Turski PA, Moritz CH, Quigley MA, Meyerand ME (2001) Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. AJNR Am J Neuroradiol 22:1326–1333.

Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF (2006) Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 103:13848–13853.

De Luca M, Beckmann CF, De Stefano N, Matthews PM, Smith SM (2006) fMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage 29:1359–1367.

De Martino F, Gentile F, Esposito F, Balsi M, Di Salle F, Goebel R, Formisano E (2007) Classification of fMRI independent components using IC-fingerprints and support vector machine classifiers. Neuroimage 34:177–194.

D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M (1995) The neural basis of the central executive system of working memory. Nature 378:279–281.

Dockery CA, Hueckel-Weng R, Birbaumer N, Plewnia C (2009) Enhancement of planning ability by transcranial direct current stimulation. J Neurosci 29:7271–7277.

Elmer S, Burkard M, Renz B, Meyer M, Jancke L (2009) Direct current induced short-term modulation of the left dorsolateral prefrontal

Table 3. Exploratory tDCS effects on RSNs: significant clusters for the contrast real tDCS > baseline1

Contrast/network	Brain area	Brodmann's area	Number of voxels	MNI coordinates		
				x	*y*	*z*
Real tDCS > baseline1						
RSNc1/default mode	L superior frontal gyrus	8	392	−24	30	44
	Posterior cingulate gyrus	23	370	0	−54	21
	L middle temporal gyrus	21	337	−62	−24	−14
	R middle temporal gyrus	21	289	68	−14	−14
	L medial frontal gyrus/anterior cingulate	10/32	201	−6	56	−10
	L parahippocampal gyrus	35	137	−20	−26	−14
RSNc2/Left frontal-parietal	R precuneus	7	271	24	−62	54
	L inferior frontal gyrus	10	219	−42	42	8
	L middle frontal gyrus	8	214	−22	28	38
	R posterior cingulate	31	130	16	−22	40
	L lingual gyrus	19	110	−20	−70	4
	L inferior parietal lobule	40	97	−60	−34	28
	R superior parietal lobule	7	67	34	−60	64
RSNc4/self-referential	L precentral/postcentral	3/4				
	Gyrus/superior parietal lobule	5/7	768	−16	−20	72
	L superior temporal gyrus	22	695	−68	−14	2
	L superior temporal gyrus	38	512	−26	16	−40
	L lingual gyrus	19	297	−28	−64	2
	R parahippocampal gyrus	30	169	28	−54	4
	L precuneus/supramarginal gyrus	7/40	133	−20	−50	38
	L cerebellum culmen		95	−34	−60	−22
	L insula	13	45	−36	−28	22
	R middle temporal gyrus	21	35	70	−12	−10
	L subgenual gyrus	25	30	−14	12	−24

Resting-state network contrast (RSNc) 1 corresponds to the contrast on the DMN, RSNc 2 to the contrast on the left FPN, RSNc 3 to the contrast on the right FPN, and RSNc 4 corresponds to the contrast of the self-referential network. Results are based on a whole-brain dual-regression approach and presented uncorrected with a $p < 0.001$ (cluster size, >20 voxels).

cortex while learning auditory presented nouns. Behav Brain Funct 5:29.

Ferrarelli F, Massimini M, Sarasso S, Casali A, Riedner BA, Angelini G, Tononi G, Pearce RA (2010) Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. Proc Natl Acad Sci U S A 107:2681–2686.

Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Salvoro B, Giacopuzzi M, Barbieri S, Priori A (2009) Transcranial direct current stimulation in severe, drug-resistant major depression. J Affect Disord 118:215–219.

Fertonani A, Rosini S, Cotelli M, Rossini PM, Miniussi C (2010) Naming facilitation induced by transcranial direct current stimulation. Behav Brain Res 208:311–318.

Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, Matthews PM, Beckmann CF, Mackay CE (2009) Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. Proc Natl Acad Sci U S A 106:7209–7214.

Fiori V, Coccia M, Marinelli CV, Vecchi V, Bonifazi S, Ceravolo MG, Provinciali L, Tomaiuolo F, Marangolo P (2011) Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic subjects. J Cogn Neurosci 23:2309–2323.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 102:9673–9678.

Fransson P (2005) Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp 26:15–29.

Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A (2006) Treatment of major depression with transcranial direct current stimulation. Bipolar Disord 8:203–204.

Gandiga PC, Hummel FC, Cohen LG (2006) Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 117:845–850.

Greicius MD, Menon V (2004) Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. J Cogn Neurosci 16:1484–1492.

Greicius MD, Krasnow B, Reiss AL, Menon V (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A 100:253–258.

Greicius MD, Supekar K, Menon V, Dougherty RF (2009) Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex 19:72–78.

Gusnard DA, Akbudak E, Shulman GL, Raichle ME (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc Natl Acad Sci U S A 98:4259–4264.

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O (2008) Mapping the structural core of human cerebral cortex. PLoS Biol 6:e159.

Hampson M, Driesen NR, Skudlarski P, Gore JC, Constable RT (2006) Brain connectivity related to working memory performance. J Neurosci 26:13338–13343.

He BJ, Snyder AZ, Vincent JL, Epstein A, Shulman GL, Corbetta M (2007) Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 53:905–918.

He BJ, Snyder AZ, Zempel JM, Smyth MD, Raichle ME (2008) Electrophysiological correlates of the brain's intrinsic large-scale functional architecture. Proc Natl Acad Sci U S A 105:16039–16044.

Hecht D, Walsh V, Lavidor M (2010) Transcranial direct current stimulation facilitates decision making in a probabilistic guessing task. J Neurosci 30:4241–4245.

Holmes CJ, Hoge R, Collins L, Woods R, Toga AW, Evans AC (1998) Enhancement of MR images using registration for signal averaging. J Comput Assist Tomogr 22:324–333.

Horovitz SG, Braun AR, Carr WS, Picchioni D, Balkin TJ, Fukunaga M, Duyn JH (2009) Decoupling of the brain's default mode network during deep sleep. Proc Natl Acad Sci U S A 106:11376–11381.

Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM (2005) Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 64:872–875.

Jang SH, Ahn SH, Byun WM, Kim CS, Lee MY, Kwon YH (2009) The effect of transcranial direct current stimulation on the cortical activation by motor task in the human brain: an fMRI study. Neurosci Lett 460:117–120.

Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17:825–841.

Jo JM, Kim YH, Ko MH, Ohn SH, Joen B, Lee KH (2009) Enhancing the working memory of stroke patients using tDCS. Am J Phys Med Rehabil 88:404–409.

Karim AA, Schneider M, Lotze M, Veit R, Sauseng P, Braun C, Birbaumer N (2010) The truth about lying: inhibition of the anterior prefrontal cortex improves deceptive behavior. Cereb Cortex 20:205–213.

Keeser D, Padberg F, Reisinger E, Pogarell O, Kirsch V, Palm U, Karch S, Möller HJ, Nitsche MA, Mulert C (2011) Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA) study. Neuroimage 55:644–657.

Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP (2008) Competition between functional brain networks mediates behavioral variability. Neuroimage 39:527–537.

Kwon YH, Ko MH, Ahn SH, Kim YH, Song JC, Lee CH, Chang MC, Jang SH (2008) Primary motor cortex activation by transcranial direct current stimulation in the human brain. Neurosci Lett 435:56–59.

Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, Rothwell JC, Lemon RN, Frackowiak RS (2005) How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? Eur J Neurosci 22:495–504.

Laufs H (2008) Endogenous brain oscillations and related networks detected by surface EEG-combined fMRI. Hum Brain Mapp 29:762–769.

Laufs H, Krakow K, Sterzer P, Eger E, Beyerle A, Salek-Haddadi A, Kleinschmidt A (2003) Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. Proc Natl Acad Sci U S A 100:11053–11058.

Lewis CM, Baldassarre A, Committeri G, Romani GL, Corbetta M (2009) Learning sculpts the spontaneous activity of the resting human brain. Proc Natl Acad Sci U S A 106:17558–17563.

Mameli F, Mrakic-Sposta S, Vergari M, Fumagalli M, Macis M, Ferrucci R, Nordio F, Consonni D, Sartori G, Priori A (2010) Dorsolateral prefrontal cortex specifically processes general-but not personal-knowledge deception: multiple brain networks for lying. Behav Brain Res 211:164–168.

Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G (2005) Breakdown of cortical effective connectivity during sleep. Science 309:2228–2232.

Mazoyer B, Houdé O, Joliot M, Mellet E, Tzourio-Mazoyer N (2009) Regional cerebral blood flow increases during wakeful rest following cognitive training. Brain Res Bull 80:133–138.

Merzagora AC, Foffani G, Panyavin I, Mordillo-Mateos L, Aguilar J, Onaral B, Oliviero A (2010) Prefrontal hemodynamic changes produced by anodal direct current stimulation. Neuroimage 49:2304–2310.

Miller KJ, Weaver KE, Ojemann JG (2009) Direct electrophysiological measurement of human default network areas. Proc Natl Acad Sci U S A 106:12174–12177.

Miranda PC, Lomarev M, Hallett M (2006) Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol 117:1623–1629.

Miranda PC, Faria P, Hallett M (2009) What does the ratio of injected current to electrode area tell us about current density in the brain during tDCS? Clin Neurophysiol 120:1183–1187.

Nichols TE, Holmes AP (2002) Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 15:1–25.

Nitsche MA, Paulus W (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 527:633–639.

Nitsche MA, Nitsche MS, Klein CC, Tergau F, Rothwell JC, Paulus W (2003) Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol 114:600–604.

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113.

Oostendorp TF, Hengeveld YA, Wolters CH, Stinstra J, van Elswijk G, Stegeman DF (2008) Modeling transcranial DC stimulation. Conf Proc IEEE Eng Med Biol Soc 2008:4226–4229.

Polanía R, Paulus W, Antal A, Nitsche MA (2011) Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. Neuroimage 54:2287–2296.

Raichle ME, Gusnard DA (2002) Appraising the brain's energy budget. Proc Natl Acad Sci U S A 99:10237–10239.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci U S A 98:676–682.

Rigonatti SP, Boggio PS, Myczkowski ML, Otta E, Fiquer JT, Ribeiro RB, Nitsche MA, Pascual-Leone A, Fregni F (2008) Transcranial direct stimulation and fluoxetine for the treatment of depression. Eur Psychiatry 23:74–76.

Sadleir RJ, Vannorsdall TD, Schretlen DJ, Gordon B (2010) Transcranial direct current stimulation (tDCS) in a realistic head model. Neuroimage 51:1310–1318.

Schacter DL, Addis DR, Buckner RL (2007) Remembering the past to imagine the future: the prospective brain. Nat Rev Neurosci 8:657–661.

Schilbach L, Eickhoff SB, Rotarska-Jagiela A, Fink GR, Vogeley K (2008) Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. Conscious Cogn 17:457–467.

Smith SM (2002) Fast robust automated brain extraction. Hum Brain Mapp 17:143–155.

Smith SM, Nichols TE (2009) Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44:83–98.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 [Suppl 1]:S208–S219.

Sparing R, Dafotakis M, Meister IG, Thirugnanasambandam N, Fink GR (2008) Enhancing language performance with non-invasive brain stimulation—a transcranial direct current stimulation study in healthy humans. Neuropsychologia 46:261–268.

Stagg CJ, O'Shea J, Kincses ZT, Woolrich M, Matthews PM, Johansen-Berg H (2009) Modulation of movement-associated cortical activation by transcranial direct current stimulation. Eur J Neurosci 30:1412–1423.

Suh HS, Lee WH, Cho YS, Kim JH, Kim TS (2010) Reduced spatial focality of electrical field in tDCS with ring electrodes due to tissue anisotropy. Conf Proc IEEE Eng Med Biol Soc 2010:2053–2056.

Turken A, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JD (2008) Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. Neuroimage 42:1032–1044.

van den Heuvel MP, Mandl RC, Kahn RS, Hulshoff Pol HE (2009) Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. Hum Brain Mapp 30:3127–3141.

van den Heuvel M, Mandl R, Luigjes J, Hulshoff Pol H (2008) Microstructural organization of the cingulum tract and the level of default mode functional connectivity. J Neurosci 28:10844–10851.

van de Ven VG, Formisano E, Prvulovic D, Roeder CH, Linden DE (2004) Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest. Hum Brain Mapp 22: 165–178.

van de Ven V, Bledowski C, Prvulovic D, Goebel R, Formisano E, Di Salle F, Linden DE, Esposito F (2008) Visual target modulation of functional connectivity networks revealed by self-organizing group ICA. Hum Brain Mapp 29:1450–1461.

Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, Zempel JM, Snyder LH, Corbetta M, Raichle ME (2007) Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447:83–86.

Volle E, Kinkingnéhun S, Pochon JB, Mondon K, Thiebaut de Schotten M, Seassau M, Duffau H, Samson Y, Dubois B, Levy R (2008) The functional architecture of the left posterior and lateral prefrontal cortex in humans. Cereb Cortex 18:2460–2469.

Wagner T, Fregni F, Fecteau S, Grodzinsky A, Zahn M, Pascual-Leone A (2007) Transcranial direct current stimulation: a computer-based human model study. Neuroimage 35:1113–1124.

Wassermann EM, Grafman J (2005) Recharging cognition with DC brain polarization. Trends Cogn Sci 9:503–505.

Wirth M, Jann K, Dierks T, Federspiel A, Wiest R, Horn H (2011) Semantic memory involvement in the default mode network: a functional neuroimaging study using independent component analysis. Neuroimage 54:3057–3066.

Zuo XN, Kelly C, Adelstein JS, Klein DF, Castellanos FX, Milham MP (2010) Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach. Neuroimage 49:2163–2177.

3 Konklusion und Ausblick

3.1 Konklusion

Zu dem Zeitpunkt unserer Publikationen hat es noch keine Arbeiten über den Effekt von präfrontaler Gleichstromstimulation auf den wachen Ruhezustand der Elektroenzephalographie bei gesunden Probanden und auf die Einwirkung während einer Arbeitsgedächtnisaufgabe gegeben. Trotz kleiner Stichproben haben unsere Studien einen wesentlichen Beitrag zum Verständnis neurophysiologischer Veränderungen nach präfrontaler tDCS erbracht. Wir konnten feststellen, dass die Erhöhung von Gedächtnisleistungen nach präfrontaler tDCS unmittelbar mit der Modulation der Elektroenzephalographie zusammenhängt. Die Tatsache der Beeinflussung der EEG-Ruhe-Aktivität konnte in Folgestudien bestätigt werden. So fanden Jacobson und Kollegen eine Reduktion der Theta-Power nach präfrontaler Gleichstromstimulation des rechten inferioren frontalen Gyrus, wo die Anode platziert wurde (Jacobson et al., 2011). Eine andere Arbeitsgruppe konnte nach dorsolateral-präfrontaler Gleichstromstimulation reduzierte Delta-Power feststellen, was unsere Ergebnisse bestätigt (Wirth et al., 2011). Indirekte Hinweise wurden auch in einer Studie an Tinnitus-Patienten gefunden. Dort zeigte die entgegengesetzte Elektrodenkonfiguration eine Erhöhung der Stromdichte im niedrigfrequenten Alpha1-Band im Bereich des subgenualen Kortex und des anterioren Cingulum (Vanneste and De Ridder, 2011). Die Reduktion der niedrigfrequenten EEG-Aktivität bei einer gleichzeitigen tendenziellen Erhöhung der höherfrequenten EEG-Aktivität könnte auf eine Steigerung der Aufmerksamkeit hinweisen (Kilner et al., 2005; Barry et al., 2009). Simultane EEG-fMRT-Arbeiten weisen auf den Zusammenhang erhöhter funktioneller Konnektivität bei dem von uns festgestellten EEG-Muster (reduzierte niedrigfrequente EEG-Aktivität, erhöhte hochfrequente EEG-Aktivität) hin (Hlinka et al., 2010; Michels et al., 2010), während die funktionelle Konnektivität sich reduzierte bei einem gleichzeitigen Anstieg der niedrigen Frequenz in der relativen EEG Power (Xu et al., 2011).

Unsere Ergebnisse der zweiten anschließend durchgeführten fMRT-basierten Studie unterstützt die Hypothese, dass präfrontale tDCS funktionelle Ruhenetz-

aktivität erhöht. Eine andere fcMRT-Arbeit zu präfrontaler tDCS, die kurz nach unserer Veröffentlichung erschienen ist, hat ebenfalls erhöhte fronto-parietale Konnektivität gefunden, begleitet von einer Deaktivierung des sogenannten ‚Default Mode Netzwerks'. In unseren unkorrigierten Ergebnissen fanden wir Deaktivierungen in anatomischen Arealen, die dem sogenannten ‚Default Mode Network' (DMN) zugeordnet werden können. Dieses Ergebnis sollte aber in Anschlussstudien mit größeren Stichproben repliziert werden. Die Erhöhung der funktionellen Konnektivität kann als möglicher Hinweis der Erleichterung und Modulation kognitiver Leistungen nach präfrontaler tDCS interpretiert werden. Erhöhte Aktivität in frontalen und parietalen Arealen während kognitiver Aufgaben und korrekter Aufgabenleistung (D'Esposito et al., 1995; Braver et al., 1997; He et al., 2007; Kelly et al., 2008; Volle et al., 2008) ist ein häufiger Studienbefund. Die präfrontale tDCS moduliert das EEG und die fcMRI und wirkt auf zerebrale neuronale Netzwerke ein. Der weitreichende Stimulationseffekt (über das Areal des präfrontalen Kortex hinaus) ist eine Erkenntnis, die zur Erklärung des Wirkmechanismus der präfrontalen tDCS beitragen wird.

3.2 Ausblick

Bildgebende Verfahren wurden erst seit kurzem als zusätzliche Erklärungsansätze erfolgreicher tDCS-Intervention in Einzelfallstudien herangezogen (Halko et al., 2011; Homan et al., 2011). Die positiven klinischen Effekte in diesen Einzelfallstudien gingen einher mit einer Veränderung des zerebralen Blutflusses (Homan et al., 2011) oder des fMRT-Signals (Halko et al., 2011). Die Vergrößerung der Stichproben in klinischen Bildgebungs- oder EEG-Studien mit Patienten ist eine wichtige Aufgabe zukünftiger Studien. Die Integration von Bildgebungsstudien mit der Magnetresonanzspektroskopie zur Feststellung der Veränderungen von Neurotransmitterkonzentrationen könnte ebenfalls wegweisend sein (Stagg et al., 2011). Eine erst sehr kurz zurückliegende Studie an Migränepatienten mit Aura kam zu dem Ergebnis, dass sowohl anodale als auch kathodale tDCS die Glutamat/Kreatin-Ratios reduzierte (Siniatchkin et al., 2011).

Auch für einen Wirknachweis von tDCS sollten in Zukunft die Stichproben klinischer Studien erhöht werden, was bereits vereinzelt umgesetzt worden ist (Vanneste et al., 2010; Fedorov et al., 2011). Ferner gibt es Hinweise, dass die Kombination von Gleichstrombehandlung mit einer zusätzlichen therapeutischen Intervention die Effekte verstärken und verlängern kann (Soler et al., 2010). Die analgetische Wirkung der tDCS in der Studie von Soler und Kollegen, in der signifikante Effekte noch nach 3 Monaten nachgewiesen werden konnten, lassen auf mögliche strukturelle Veränderungen schließen, worauf es im Rattenmodell bereits erste Hinweise gegeben hat (Kim et al., 2010). Künftige Studien sollten demnach auch nach längerer Stimulationsdauer die strukturelle Konnektivität hinsichtlich neuroplastischer Veränderungen untersuchen.

Literaturverzeichnis

Andrews SC, Hoy KE, Enticott PG, Daskalakis ZJ, Fitzgerald PB (2011) Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimul 4:84-89.

Antal A, Polania R, Schmidt-Samoa C, Dechent P, Paulus W (2011) Transcranial direct current stimulation over the primary motor cortex during fMRI. Neuroimage 55:590-596.

Ardolino G, Bossi B, Barbieri S, Priori A (2005) Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. J Physiol 568:653-663.

Arul-Anandam AP, Loo C, Martin D, Mitchell PB (2009) Chronic neuropathic pain alleviation after transcranial direct current stimulation to the dorsolateral prefrontal cortex. Brain Stimul 2:149-151.

Baker JM, Rorden C, Fridriksson J (2010) Using transcranial direct-current stimulation to treat stroke patients with aphasia. Stroke 41:1229-1236.

Barry RJ, Clarke AR, Johnstone SJ, Brown CR (2009) EEG differences in children between eyes-closed and eyes-open resting conditions. Clin Neurophysiol 120:1806-1811.

Baudewig J, Nitsche MA, Paulus W, Frahm J (2001) Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. Magn Reson Med 45:196-201.

Beeli G, Casutt G, Baumgartner T, Jancke L (2008a) Modulating presence and impulsiveness by external stimulation of the brain. Behav Brain Funct 4:33.

Beeli G, Koeneke S, Gasser K, Jancke L (2008b) Brain stimulation modulates driving behavior. Behav Brain Funct 4:34.

Bikson M, Inoue M, Akiyama H, Deans JK, Fox JE, Miyakawa H, Jefferys JG (2004) Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. J Physiol 557:175-190.

Bindman LJ, Lippold OC, Redfearn JW (1964) The Action of Brief Polarizing Currents on the Cerebral Cortex of the Rat (1) During Current Flow and (2) in the Production of Long-Lasting after-Effects. J Physiol 172:369-382.

Boggio PS, Zaghi S, Fregni F (2009a) Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia 47:212-217.

Boggio PS, Zaghi S, Lopes M, Fregni F (2008a) Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur J Neurol 15:1124-1130.

Boggio PS, Khoury LP, Martins DC, Martins OE, de Macedo EC, Fregni F (2009b) Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. J Neurol Neurosurg Psychiatry 80:444-447.

Boggio PS, Zaghi S, Villani AB, Fecteau S, Pascual-Leone A, Fregni F (2010a) Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Drug Alcohol Depend 112:220-225.

Boggio PS, Campanha C, Valasek CA, Fecteau S, Pascual-Leone A, Fregni F (2010b) Modulation of decision-making in a gambling task in older adults with transcranial direct current stimulation. Eur J Neurosci 31:593-597.

Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, Fregni F (2008b) A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol 11:249-254.

Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC (1997) A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5:49-62.

Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F (2011) A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol 14:1133-1145.

Cerruti C, Schlaug G (2009) Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. J Cogn Neurosci 21:1980-1987.

Creutzfeldt O, Struck G (1962) [Neurophysiology and morphology of the chronically isolated cortical islet in the cat: brain potentials and neuron activity of an isolated nerve cell population without afferent fibers]. Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr 203:708-731.

Creutzfeldt OD, Fromm GH, Kapp H (1962) Influence of transcortical d-c currents on cortical neuronal activity. Exp Neurol 5:436-452.

D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M (1995) The neural basis of the central executive system of working memory. Nature 378:279-281.

Dell'osso B, Zanoni S, Ferrucci R, Vergari M, Castellano F, D'Urso N, Dobrea C, Benatti B, Arici C, Priori A, Altamura AC (2011) Transcranial direct current stimulation for the outpatient treatment of poor-responder depressed patients. Eur Psychiatry (in press).

Dockery CA, Hueckel-Weng R, Birbaumer N, Plewnia C (2009) Enhancement of planning ability by transcranial direct current stimulation. J Neurosci 29:7271-7277.

Elmer S, Burkard M, Renz B, Meyer M, Jancke L (2009) Direct current induced short-term modulation of the left dorsolateral prefrontal cortex while learning auditory presented nouns. Behav Brain Funct 5:29.

Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A (2007a) Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. J Neurosci 27:12500-12505.

Fecteau S, Pascual-Leone A, Zald DH, Liguori P, Theoret H, Boggio PS, Fregni F (2007b) Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. J Neurosci 27:6212-6218.

Fedorov A, Jobke S, Bersnev V, Chibisova A, Chibisova Y, Gall C, Sabel BA (2011) Restoration of vision after optic nerve lesions with noninvasive transorbital alternating current stimulation: a clinical observational study. Brain Stimul 4:189-201.

Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Salvoro B, Giacopuzzi M, Barbieri S, Priori A (2009) Transcranial direct current stimulation in severe, drug-resistant major depression. J Affect Disord 118:215-219.

Fertonani A, Rosini S, Cotelli M, Rossini PM, Miniussi C (2010) Naming facilitation induced by transcranial direct current stimulation. Behav Brain Res 208:311-318.

Feurra M, Bianco G, Santarnecchi E, Del Testa M, Rossi A, Rossi S (2011) Frequency-dependent tuning of the human motor system induced by transcranial oscillatory potentials. J Neurosci 31:12165-12170.

Frank E, Schecklmann M, Landgrebe M, Burger J, Kreuzer P, Poeppl TB, Kleinjung T, Hajak G, Langguth B (2011) Treatment of chronic tinnitus with repeated sessions of prefrontal transcranial direct current stimulation: outcomes from an open-label pilot study. J Neurol (in press).

Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A (2006) Treatment of major depression with transcranial direct current stimulation. Bipolar Disord 8:203-204.

Halko MA, Datta A, Plow EB, Scaturro J, Bikson M, Merabet LB (2011) Neuroplastic changes following rehabilitative training correlate with regional electrical field induced with tDCS. Neuroimage 57:885-891.

Hammer A, Mohammadi B, Schmicker M, Saliger S, Munte TF (2011) Errorless and errorful learning modulated by transcranial direct current stimulation. BMC Neurosci 12:72.

He BJ, Snyder AZ, Vincent JL, Epstein A, Shulman GL, Corbetta M (2007) Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 53:905-918.

Hlinka J, Alexakis C, Diukova A, Liddle PF, Auer DP (2010b) Slow EEG pattern predicts reduced intrinsic functional connectivity in the default mode network: an inter-subject analysis. Neuroimage 53:239-246.

Homan P, Kindler J, Federspiel A, Flury R, Hubl D, Hauf M, Dierks T (2011) Muting the voice: a case of arterial spin labeling-monitored transcranial direct current stimulation treatment of auditory verbal hallucinations. Am J Psychiatry 168:853-854.

Islam N, Aftabuddin M, Moriwaki A, Hattori Y, Hori Y (1995) Increase in the calcium level following anodal polarization in the rat brain. Brain Res 684:206-208.

Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM (2005) Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 64:872-875.

Jacobson L, Ezra A, Berger U, Lavidor M (2011) Modulating oscillatory brain activity correlates of behavioral inhibition using transcranial direct current stimulation. Clin Neurophysiol (in press).

Jang SH, Ahn SH, Byun WM, Kim CS, Lee MY, Kwon YH (2009) The effect of transcranial direct current stimulation on the cortical activation by motor task in the human brain: an fMRI study. Neurosci Lett 460:117-120.

Javadi AH, Walsh V (2011) Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory. Brain Stimul (in press).

Javadi AH, Cheng P, Walsh V (2011) Short duration transcranial direct current stimulation (tDCS) modulates verbal memory. Brain Stimul (in press).

Jo JM, Kim YH, Ko MH, Ohn SH, Joen B, Lee KH (2009) Enhancing the working memory of stroke patients using tDCS. Am J Phys Med Rehabil 88:404-409.

Kanai R, Chaieb L, Antal A, Walsh V, Paulus W (2008) Frequency-dependent electrical stimulation of the visual cortex. Curr Biol 18:1839-1843.

Keeser D, Padberg F, Reisinger E, Pogarell O, Kirsch V, Palm U, Karch S, Moller HJ, Nitsche MA, Mulert C (2011a) Prefrontal direct current stimulation modulates

resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA) study. Neuroimage 55:644-657.

Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, Brunelin J, Moller HJ, Reiser M, Padberg F (2011b) Prefrontal Transcranial Direct Current Stimulation Changes Connectivity of Resting-State Networks during fMRI. J Neurosci 31:15284-15293.

Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP (2008) Competition between functional brain networks mediates behavioral variability. Neuroimage 39:527-537.

Kilner JM, Mattout J, Henson R, Friston KJ (2005) Hemodynamic correlates of EEG: a heuristic. Neuroimage 28:280-286.

Kim SJ, Kim BK, Ko YJ, Bang MS, Kim MH, Han TR (2010) Functional and histologic changes after repeated transcranial direct current stimulation in rat stroke model. J Korean Med Sci 25:1499-1505.

Kirov R, Weiss C, Siebner HR, Born J, Marshall L (2009) Slow oscillation electrical brain stimulation during waking promotes EEG theta activity and memory encoding. Proc Natl Acad Sci U S A 106:15460-15465.

Knoch D, Nitsche MA, Fischbacher U, Eisenegger C, Pascual-Leone A, Fehr E (2008) Studying the neurobiology of social interaction with transcranial direct current stimulation--the example of punishing unfairness. Cereb Cortex 18:1987-1990.

Laird AR, Fox PM, Eickhoff SB, Turner JA, Ray KL, McKay DR, Glahn DC, Beckmann CF, Smith SM, Fox PT (2011a) Behavioral interpretations of intrinsic connectivity networks. J Cogn Neurosci 23:4022-4037.

Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, Rothwell JC, Lemon RN, Frackowiak RS (2005) How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? Eur J Neurosci 22:495-504.

Liebetanz D, Fregni F, Monte-Silva KK, Oliveira MB, Amancio-dos-Santos A, Nitsche MA, Guedes RC (2006a) After-effects of transcranial direct current stimulation (tDCS) on cortical spreading depression. Neurosci Lett 398:85-90.

Liebetanz D, Klinker F, Hering D, Koch R, Nitsche MA, Potschka H, Loscher W, Paulus W, Tergau F (2006b) Anticonvulsant effects of transcranial direct-current stimulation (tDCS) in the rat cortical ramp model of focal epilepsy. Epilepsia 47:1216-1224.

Loo CK, Sachdev P, Martin D, Pigot M, Alonzo A, Malhi GS, Lagopoulos J, Mitchell P (2010) A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. Int J Neuropsychopharmacol 13:61-69.

Marshall L, Molle M, Hallschmid M, Born J (2004) Transcranial direct current stimulation during sleep improves declarative memory. J Neurosci 24:9985-9992.

Marshall L, Kirov R, Brade J, Molle M, Born J (2011) Transcranial electrical currents to probe EEG brain rhythms and memory consolidation during sleep in humans. PLoS ONE 6:e16905.

Martin DM, Alonzo A, Mitchell PB, Sachdev P, Galvez V, Loo CK (2011) Fronto-extracephalic transcranial direct current stimulation as a treatment for major depression: an open-label pilot study. J Affect Disord 134:459-463.

Mendonca ME, Santana MB, Baptista AF, Datta A, Bikson M, Fregni F, Araujo CP (2011) Transcranial DC stimulation in fibromyalgia: optimized cortical target supported by high-resolution computational models. J Pain 12:610-617.

Merzagora AC, Foffani G, Panyavin I, Mordillo-Mateos L, Aguilar J, Onaral B, Oliviero A (2010) Prefrontal hemodynamic changes produced by anodal direct current stimulation. Neuroimage 49:2304-2310.

Michels L, Bucher K, Luchinger R, Klaver P, Martin E, Jeanmonod D, Brandeis D (2010) Simultaneous EEG-fMRI during a working memory task: modulations in low and high frequency bands. PLoS ONE 5:e10298.

Miranda PC, Lomarev M, Hallett M (2006) Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol 117:1623-1629.

Mulquiney PG, Hoy KE, Daskalakis ZJ, Fitzgerald PB (2011) Improving working memory: Exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. Clin Neurophysiol 122:2384-2389.

Nitsche MA, Paulus W (2001) Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57:1899-1901.

Nitsche MA, Nitsche MS, Klein CC, Tergau F, Rothwell JC, Paulus W (2003a) Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol 114:600-604.

Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W (2003b) Modulation of cortical excitability by weak direct current stimulation--technical, safety and functional aspects. Suppl Clin Neurophysiol 56:255-276.

Nitsche MA, Niehaus L, Hoffmann KT, Hengst S, Liebetanz D, Paulus W, Meyer BU (2004) MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. Clin Neurophysiol 115:2419-2423.

Nitsche MA, Roth A, Kuo MF, Fischer AK, Liebetanz D, Lang N, Tergau F, Paulus W (2007) Timing-dependent modulation of associative plasticity by general network excitability in the human motor cortex. J Neurosci 27:3807-3812.

Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, Henning S, Tergau F, Paulus W (2003c) Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol 553:293-301.

Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, Paulus W, Hummel F, Boggio PS, Fregni F, Pascual-Leone A (2008) Transcranial direct current stimulation: State of the art 2008. Brain Stimul 1:206-223.

Palm U, Schiller C, Fintescu Z, Obermeier M, Keeser D, Reisinger E, Pogarell O, Nitsche MA, Moller HJ, Padberg F (2011) Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. Brain Stimul (in press).

Paquette C, Sidel M, Radinska BA, Soucy JP, Thiel A (2011) Bilateral transcranial direct current stimulation modulates activation-induced regional blood flow changes during voluntary movement. J Cereb Blood Flow Metab 31:2086-2095.

Pena-Gomez C, Sala-Lonch R, Junque C, Clemente IC, Vidal D, Bargallo N, Falcon C, Valls-Sole J, Pascual-Leone A, Bartres-Faz D (2011) Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. Brain Stimul (in press).

Pfurtscheller G (1970) [Changes in the evoked and spontaneous brain activity of man during extracranial polarization]. Z Gesamte Exp Med 152:284-293.

Pogosyan A, Gaynor LD, Eusebio A, Brown P (2009) Boosting cortical activity at Beta-band frequencies slows movement in humans. Curr Biol 19:1637-1641.

Polania R, Paulus W, Nitsche MA (2011a) Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum Brain Mapp (in press).

Polania R, Paulus W, Antal A, Nitsche MA (2011b) Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. Neuroimage 54:2287-2296.

Poreisz C, Boros K, Antal A, Paulus W (2007) Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull 72:208-214.

Purpura DP, McMurtry JG (1965) Intracellular Activities and Evoked Potential Changes during Polarization of Motor Cortex. J Neurophysiol 28:166-185.

Radman T, Ramos RL, Brumberg JC, Bikson M (2009) Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. Brain Stimul 2:215-228, 228 e211-213.

Reato D, Rahman A, Bikson M, Parra LC (2010) Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci 30:15067-15079.

Rigonatti SP, Boggio PS, Myczkowski ML, Otta E, Fiquer JT, Ribeiro RB, Nitsche MA, Pascual-Leone A, Fregni F (2008) Transcranial direct stimulation and fluoxetine for the treatment of depression. Eur Psychiatry 23:74-76.

Siniatchkin M, Sendacki M, Moeller F, Wolff S, Jansen O, Siebner H, Stephani U (2011) Abnormal Changes of Synaptic Excitability in Migraine with Aura. Cereb Cortex (in press).

Soler MD, Kumru H, Pelayo R, Vidal J, Tormos JM, Fregni F, Navarro X, Pascual-Leone A (2010) Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. Brain 133:2565-2577.

Stagg CJ, Bachtiar V, Johansen-Berg H (2011) The Role of GABA in Human Motor Learning. Curr Biol 21:480-484.

Stagg CJ, O'Shea J, Kincses ZT, Woolrich M, Matthews PM, Johansen-Berg H (2009a) Modulation of movement-associated cortical activation by transcranial direct current stimulation. Eur J Neurosci 30:1412-1423.

Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, Morris PG, Matthews PM, Johansen-Berg H (2009b) Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci 29:5202-5206.

Suh HS, Kim SH, Lee WH, Kim TS (2009) Realistic simulation of transcranial direct current stimulation via 3-d high-resolution finite element analysis: Effect of tissue anisotropy. Conf Proc IEEE Eng Med Biol Soc 2009:638-641.

Takano Y, Yokawa T, Masuda A, Niimi J, Tanaka S, Hironaka N (2011) A rat model for measuring the effectiveness of transcranial direct current stimulation using fMRI. Neurosci Lett 491:40-43.

Teo F, Hoy KE, Daskalakis ZJ, Fitzgerald PB (2011) Investigating the Role of Current Strength in tDCS Modulation of Working Memory Performance in Healthy Controls. Front Psychiatry 2:45.

Valle A, Roizenblatt S, Botte S, Zaghi S, Riberto M, Tufik S, Boggio PS, Fregni F (2009) Efficacy of anodal transcranial direct current stimulation (tDCS) for the treatment of fibromyalgia: results of a randomized, sham-controlled longitudinal clinical trial. J Pain Manag 2:353-361.

Vanneste S, De Ridder D (2011) Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity. Eur J Neurosci 34:605-614.

Vanneste S, Plazier M, Ost J, van der Loo E, Van de Heyning P, De Ridder D (2010) Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study. Exp Brain Res 202:779-785.

Vercammen A, Rushby JA, Loo C, Short B, Weickert CS, Weickert TW (2011) Transcranial direct current stimulation influences probabilistic association learning in schizophrenia. Schizophr Res 131:198-205.

Volle E, Kinkingnehun S, Pochon JB, Mondon K, Thiebaut de Schotten M, Seassau M, Duffau H, Samson Y, Dubois B, Levy R (2008) The functional architecture of the left posterior and lateral prefrontal cortex in humans. Cereb Cortex 18:2460-2469.

Wachter D, Wrede A, Schulz-Schaeffer W, Taghizadeh-Waghefi A, Nitsche MA, Kutschenko A, Rohde V, Liebetanz D (2011) Transcranial direct current stimulation induces polarity-specific changes of cortical blood perfusion in the rat. Exp Neurol 227:322-327.

Wagner T, Valero-Cabre A, Pascual-Leone A (2007a) Noninvasive human brain stimulation. Annu Rev Biomed Eng 9:527-565.

Wagner T, Fregni F, Fecteau S, Grodzinsky A, Zahn M, Pascual-Leone A (2007b) Transcranial direct current stimulation: a computer-based human model study. Neuroimage 35:1113-1124.

Wirth M, Jann K, Dierks T, Federspiel A, Wiest R, Horn H (2011a) Semantic memory involvement in the default mode network: A functional neuroimaging study using independent component analysis. Neuroimage 54:3057-3066.

Xu F, Uh J, Brier MR, Hart J, Jr., Yezhuvath US, Gu H, Yang Y, Lu H (2011) The influence of carbon dioxide on brain activity and metabolism in conscious humans. J Cereb Blood Flow Metab 31:58-67.

Zaehle T, Rach S, Herrmann CS (2010) Transcranial alternating current stimulation enhances individual alpha activity in human EEG. PLoS ONE 5:e13766.

Zaehle T, Sandmann P, Thorne JD, Jancke L, Herrmann CS (2011) Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: Combined behavioural and electrophysiological evidence. BMC Neurosci 12:2.

Lebenslauf/Vita

ANGABEN ZUR PERSON

Name	**Keeser, Daniel**
E-mail	**daniel.keeser@med.uni-muenchen.de**
	keeser@lrz.tu-muenchen.de
Internet	*www.interest-imaging.de*
Familienstand	ledig
Geburtsdatum/- ort	04.01.77, München

SCHULBILDUNG

•1993 - 1998	Gisela-Gymnasium, München
• Erworbene Qualifikation	Allgemeine Hochschulreife

STUDIUM

• 2001 - 2006	Universität, Konstanz
• Erworbene Qualifikation	Diplom Psychologie, Gesamtnote: 1
• Diplomarbeitsthema	Elektrophysiologische Untersuchung bei Jungen mit Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS), Note 1

PRAKTIKA

• 10.2003 - 03.2004	Vollzeit-Praktikum in der Arbeitsgruppe Kognitive Neurologie/Neuropsychologie – Klinikum Großhadern, München Tätigkeit: Neuropsychologische Diagnostik, Aufbau einer neuropsychologischen Datenbank

BERUFSERFAHRUNG

•seit 12/2007	PhD Student, Forschungsgruppe Transkranielle Hirnstimulation und Neuroplastizität & Abteilung für Klinische Neurophysiologie und Forschungsgruppe Hirnfunktionsdiagnostik Klinik für Psychiatrie und Psychotherapie der LMU *http://psywifo.klinikum.uni-muenchen.de/forschung/tms/index.html*
• 8/2008 – 3/2011	Wissenschaftlicher Angestellter (50%) Schmerztherapie- und Forschung Zentrum für interdisziplinäre Schmerztherapie Neurologische Klinik, Klinikum r.d. Isar

Technische Universität München

• 8/2009 – 3/2011	Honorarkraft (wissenschaftl. Mitarbeiter), Radiologie, Klinikum Innenstadt
•seit 01/2009	Ausbildung zum Psychologischen Psychotherapeuten (CIP)
•9/2010	Bestandene Zwischenprüfung zum Psychologischen Psychotherapeuten (VT)
• 5/2011 – 3/2012	Wissenschaftliche Mitarbeit bei Epionics

VERÖFFENTLICHUNGEN

VORTRÄGE

26.02.2009
Keeser, D
Neue Analysetechniken – Implikationen für Forschung und Klinik
Münchner EEG-Tage 2009

27.02.2009
Keeser, D
Quantitatives EEG bei ADHS
Münchner EEG-Tage 2009

20.03.2009
Keeser, D
Klinik und Grundlagen von akuten und chronischen Schmerzen
M.E.G. Jahrestagung, Bad Kissingen

26.03.2009
Keeser, D
Teipel, S, Meindl, T, Medvedeva, A, Karch, S, Leicht, G, Möller, H J, Reiser, M, Mulert, C, Pogarell, O:
Functional connectivity in patients with early Alzheimers disease, MCI and healthy controls assessed by fMRI and EEG
53. Jahrestagung der Deutschen Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung
Klinische Neurophysiologie 40(1): 50-51

31.07.2009
Keeser, D
Bor, J, Meindl, T, Mulert, C, Pogarell, O, Möller, HJ, Reiser, M & Padberg, F.
Prefrontal transcranial Direct Current Stimulation (tDCS) modulates resting-state functional connectivity in healthy subjects: a functional magnetic resonance imaging (fMRI) study
Research Festival 2009

25.02.2010
Keeser, D
Neue Analysetechniken, Gehirnstimulation (tDCS, Neurofeedback) und die Auswirkungen auf das EEG/fMRT
Münchner EEG-Tage 2010

07.07.2011
Keeser, D
Die Wirkung präfrontaler tDCS auf EEG und fMRT-

Ruhenetzwerke
2. Jahrestagung der Deutschen Gesellschaft für Hirnstimulation (Münster)

ABSTRACTS

Keeser, D, Reisinger, E, Palm, U, Fintescu, Z, Schiller, C, Mulert, C & Padberg, F. Effect of prefrontal transcranial Direct Current Stimulation (tDCS) on standardized Low Resolution Tomography (sLORETA) in healthy subjects. *Int J Neuropsychopharmacol* 2008;11(S1):101.

Palm U, Keeser D, Schiller C, Fintescu Z, Reisinger E, Mulert C, Pogarell O, Möller H-J, Padberg F. Transcranial direct current stimulation (tDCS) in therapy-resistant depression: Preliminary results from a double-blind, placebo-controlled study. *Int J Neuropsychopharmacol* 2008: 11 (S1): 188.

Palm, U, Keeser, D, Schiller, C, Fintescu, Z, Reisinger, E, Mulert, C, Pogarell, O, Möller, H-J, Padberg, F.
Transcranial direct current stimulation in therapy-resistant depression: Preliminary results from a double-blind, placebo-controlled study
Brain Stimulation, Vol.1(3): 241-242.

Keeser, D, Mulert, C, Reisinger, E, Palm, U, Pogarell, O, Fintescu, Z, Schiller, C, Möller, H J, Nitsche, M, Padberg, F.
Effect of prefrontal transcranial direct current stimulation on standardized low resolution tomography in healthy subjects
Klinische Neurophysiologie 40 (1): 78

Keeser, D, Tiemann, L, Valet, M, Schulz, E, Ploner, M, Kalckreuth, A, Padberg, F, Toelle, T:
Preliminary EEG and low resolution electromagnetic tomography correlates of migraine therapy
Klinische Neurophysiologie 40 (1): 81

Palm, U, Keeser, D, Fintescu, Z, Schiller, C, Reisinger, E, Mulert, C, Pogarell, O, Möller, H J, Padberg, F.
Transcranial direct current stimulation in therapy-resistant depression: a double-blind, placebo-controlled study
Klinische Neurophysiologie 40 (1): 98

Padberg, F, Grossheinrich, N, Keeser, D, Holzer, M, Mulert, C, Reinl, M, Pogarell, O.
New protocols of non-invasive brain stimulation: Enhancing the after-effect.
9th World Congress of Biological Psychiatry, 28.6.-2.7.2009

Palm, U, Keeser, D, Fintescu, Z, Schiller, C, Reisinger, E, Mulert, C, Pogarell, O, Möller, H-J, Padberg, F.
Transcranial direct current stimulation (tDCS) in therapy-resistant depression: A double-blind, placebo-controlled study.
9th World Congress of Biological Psychiatry, 28.6.-2.7.2009

Bor, J, Keeser, D, Meindl, T, Mulert, C, Palm, U, Brunelin, J,
Pogarell, O, Möller, H-J, Reiser, M, Padberg, F.
Prefrontal transcranial Direct Current Stimulation (tDCS) modulates resting-state functional connectivity in healthy subjects: A functional magnetic resonance imaging (fMRI) study.
9th World Congress of Biological Psychiatry, 28.6.-2.7.2009

Palm U, Fintescu Z, Schiller C, Reisinger E, Keeser D, Bondy B, Padberg F. BDNF plasma level changes after transcranial direct current stimulation in major depressive disorder. *Pharmacopsychiatry* 2009;42:235.

Padberg, F, Holzer, M, Keeser, D, Palm, U, Riedel, M, Möller, H-J, Pogarell, O.
Intermittierende transkranielle Kortexstimulation (rTMS und tDCS) für die Akut- und Langzeittherapie von Depressionen.
DGPPN Kongress, 25.-28.11.2009 Berlin.

Padberg, F, Keeser, D, Palm, U, Holzer, M, Mulert, C, Riedel, M, Möller, H-J, Pogarell, O.
rTMS und tDCS: Intermittierende Stimulation und Neuroplastizität
DGPPN Kongress, 25.-28.11. Berlin.

Keeser, D, Meindl, T, Bor, J, Esposito, F, Reiser, M, Palm, U, Pogarell, O, Mulert, C & Padberg, F.
Prefrontal transcranial Direct Current Stimulation (tDCS) modulates resting-state functional connectivity in healthy subjects: a functional magnetic resonance imaging (fMRI) study.
16th Human Brain Mapping Congress, 6-10.6.2010, Barcelona, Espania.

Meindl, T, Keeser, D, Pogarell, O, Reiser, M, Teipel, S.
Functional connectivity in patients with dementia assessed by resting state fMRI and EEG
16th Human Brain Mapping Congress, 6-10.6.2010, Barcelona, Espania

Keeser, D, Meindl, T, Bor, J, Esposito, F, Reiser, M, Palm, U, Pogarell, O, Mulert, C & Padberg, F.
Prefrontal transcranial Direct Current Stimulation (tDCS) mudulates resting-state functional connectivity in healthy subjects: a functional magnetic resonance imaging (fMRI) study.
Kongress der Deutschen Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde, 24. - 27.11.2010, Berlin

Palm U, Keeser D, Schiller C, Fintescu Z, Reisinger E, Mulert C, Pogarell O, Möller H-J, Padberg F. Transcranial direct current stimulation (tDCS) in therapy-resistant depression: a double-blind, placebo-controlled study. In: Abstract Book of the DGPPN congress 2010. German Association for Psychiatry and Psychotherapy, Berlin, 2010.

Keeser, D, Meindl, T, Bor, J, Esposito, F, Reiser, M, Palm, U, Pogarell, O, Mulert, C & Padberg, F. Prefrontal transcranial direct current stimulation (tDCS) modulates resting-state functional connectivity. In: Abstract Book of the DGPPN congress 2010. German Association for Psychiatry and Psychotherapy, Berlin, 2010.

Mueller, S, Keeser, D, Hegenloh, M, Hennig-Fast, K, Samson, A, Coates, U, Reiser, MF, Meindl, T.
Aberrant functional and structural brain connectivity in autism: Evidence from resting state fMRI in combination with DTI in Asperger's Syndrome.
RSNA Congress, 28.11.- 3.12. 2010, Chicago

Mueller, S, Keeser, D, Fuchs, C, Hennig-Fast, K, Coates, U, Reiser, MF, Meindl, T.
Aberrant functional connectivity in schizophrenic patients during acute and post psychotic episodes. Evidence from resting state fMRI in combination with DTI.

RSNA Congress, 28.11.- 3.12. 2010, Chicago

Mueller, S, Keeser, D, Samson, A, Hennig-Fast, K, Coates, U, Reiser, MF, Meindl, T. Alterations in functional and structural connectivity provide correlates for symptoms in autism.
17th Human Brain Mapping Congress, 26-30.6.2011, Quebec, Kanada.

Mueller, S, Keeser, D, Hennig-Fast, K, Fuchs, C, Coates, U, Reiser, MF, Meindl, T. Alterations in functional and structural connectivity in paranoid schizophrenia.
17th Human Brain Mapping Congress, 26-30.6.2011, Quebec, Kanada.

Blautzik, J, Keeser, D, Berman, A, Paolini, M, Kirsch, V, Mueller, S, Reiser, M, Teipel, SJ, Meindl, T. Test-retest reliability of resting-state networks in healthy elderly subjects and MCI patients.
24th European Congress of Radiology, 1-5.3.2012, Vienna, Austria.

PUBLIKATIONEN

Palm, U, Keeser, D, Schiller, C, Fintescu, Z, Reisinger, E, Nitsche, M, Padberg, F (2008a). Skin lesions after treatment with transcranial direct current stimulation(tDCS). *Brain Stimulation 1*, 386-387

Palm, U, Keeser, D, Schiller, C, Fintescu, Z, Reisinger, E, Baghai, TC, Mulert, C, Padberg, F (2009). Transcranial direct current stimulation in a patient with therapy-resistant major depression. *World J Biol Psychiatry* 10 (5): 632-635.

Keeser, D & Padberg, F. Transcranial Direct Current Stimulation. *Neuroconnections*, January, 2009.

Engelbregt, HJ, Kok, G, Vis, R, Keeser, D & Deijen, JB.Instrumentele Conditionering van frontaalkwab activiteit bij gezonde jong-volwassen – Een dubbelblind placebogecontroleerd onderzoek naar EEG-neurofeedback (2010). *Dutch Journal of Neuropsychology* 5 (1).[1]

Keeser D, Padberg F, Reisinger E, Pogarell O, Kirch V, Palm U, Karch S, Möller HJ, Nitsche MA, Mulert C (2011). Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: A standardized low resolution tomography (sLORETA) study. *NeuroImage* 55(2): 644-657.

Keeser, D, Bor, J, Meindl, T, Reiser, M, Palm, U, Pogarell, O, Mulert, C & Padberg, F. Prefrontal transcranial Direct Current Stimulation (tDCS) mudulates resting-state functional connectivity in healthy subjects: a functional magnetic resonance imaging (fMRI) study. *Journal of Neuroscience*. 2011 Oct 26;31(43):15284-93.

Palm, U, Schiller, C, Fintescu, Z, Obermeier, M, Keeser, D, Reisinger, E, Pogarell, O, Nitsche, M.A, Möller, H-J and Padberg F
Transcranial direct current stimulation in therapy-resistant depression: A double-blind, placebo-controlled study. Brain Stimulation (2011) epub. Sept 7.

[1] Die Hauptpublikation ist in Planung für ein internationales Journal.

Mueller, S, Keeser, D, Teipel, S, Meindl, T.
Functional and structural magnetic resonance imaging in neuropsychiatric disorders, **Part 1**: imaging techniques and their application in mild cognitive impairment and Alzheimer's disease. *American Journal of Neuroradiology (2011)* epub. Dec 15.

Mueller, S, Keeser, D, Teipel, S, Meindl, T.
Functional and structural magnetic resonance imaging in neuropsychiatric disorders, **Part 2**: application in schizophrenia and autism. *American Journal of Neuroradiology* (2011) epub. Dec 15.

Engelbregt, HJ, Keeser, D, Promes, VHL, Schouten-Verhagen, S, Deijen, JB (2012).
In-vivo EEG changes during a panic attack in a patient with specific phobia. *Journal of Medical Cases* 3 (1): 34-38.

Gürkov, R, Flatz, W, Keeser, D, Strupp, M, Ertl-Wagner, B, Krause, E.
Effect of standard-dose Betahistine on endolymphatic hydrops: an MRI pilot study. *Eur Arch Otorhinolaryngol*. (2012) epub. Jul 4.

Danksagung

Mein besonderer Dank gilt PD Frank Padberg, der mich die gesamte Zeit meiner Dissertation in jeder Hinsicht unterstützt hat. Ohne seine unersetzbare fachliche, moralische und wissenschaftliche Unterstützung wäre diese kumulative Promotion nicht zu realisieren gewesen. Ein großer und herzlicher Dank geht an meine Partnerin Bianca, die immer für mich dagewesen ist und demnach einen großen Anteil am Zustandekommen dieser Arbeit hatte. Die Unterstützung durch meine Eltern ist unersetzbar und ich bin ihnen unendlich dankbar dafür. Die Arbeit mit PD Dr. Thomas Meindl ist durchgehend inspirierend, unterstützend und kollegial gewesen und setzt sich bis heute fort. Bei Prof. Dr. Mulert möchte ich mich ebenfalls bedanken, seine Hilfe und sein umfassendes Wissen der Neurophysiologie sind eine große Hilfe gewesen. Dr. Ulrich Palm hat mich die letzten Jahre stark unterstützt und er hatte einen wesentlichen Anteil an der Etablierung der transkraniellen Gleichstromstimulation in der Psychiatrischen Klinik an der Nußbaumstrasse in München. Last but not least möchte ich mich bedanken bei PD Dr. Oliver Pogarell und Valerie Kirsch von denen ich viel Unterstützung erfahren habe. Ferner gilt mein Dank PD Dr. Michael Nitsche, Prof. Möller, Prof. Reiser, Eva Reisinger, Zoe Fintescu und Christina Schiller, die alle an den Arbeiten beteiligt gewesen sind.