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Reprint of: Transcranial direct current stimulation (tDCS) – Application in neuropsychology ☆

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ABSTRACT

Non-invasive brain stimulation is a versatile tool to modulate psychological processes via alterations of brain activity, and excitability. It is applied to explore the physiological basis of cognition and behavior, as well as to reduce clinical symptoms in neurological and psychiatric diseases. Neuromodulatory brain stimulation via transcranial direct currents (tDCS) has gained increased attention recently. In this review we will describe physiological mechanisms of action of tDCS, and summarize its application to modulate psychological processes in healthy humans and neuropsychiatric diseases. Furthermore, beyond giving an overview of the state of the art of tDCS, including limitations, we will outline future directions of research in this relatively young scientific field.

1. Introduction

In the last years, the physiological foundation of psychological processes and behavior has been increasingly explored not only in animal models, but also directly in the human brain. Non-invasive neuroimaging, and stimulation techniques – such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), magnetoencephalography (MEG) and transcranial magnetic stimulation (TMS) – have largely enhanced our comprehension of task-related physiological alterations with regard to regional activity and excitability alterations, and oscillatory brain activity, as well as interregional communication between distant brain areas, such as functional connectivity (Mather et al., 2013; Wixted and Mickes, 2013). Beyond studies in healthy humans, pathological alterations of cortical activity and excitability have been increasingly identified as important factors in neuropsychiatric diseases, involved in a broad variety of clinical symptoms (Cramer et al., 2011; Stam and Van Straaten, 2012).

Whereas neuroimaging is crucial for identification of task-related physiological alterations, it is in many cases not easy to identify the respective causal contribution to specific functions. Here non-invasive brain stimulation comes into play. If modulation of task-related cortical activity results in functional alterations, this is a strong hint for causality. Moreover, *fostering* respective physiological processes might also be able to improve psychological and behavioral processes in health and disease (Flöel, 2014; Kuo et al., 2014; Kuo and Nitsche, 2012). In the last years, various non-invasive brain stimulation techniques have been developed which enable the modulation of cortical excitability and activity (Ziemann et al., 2008), and result in functional alterations of psychological, and behavioral processes (Flöel, 2014; Kuo et al., 2014; Kuo and Nitsche, 2012). Transcranial direct current stimulation (tDCS) is one of these techniques. It was already shown about 50 years ago that application of relatively weak, subthreshold direct currents over the cerebral cortex of animals induces polarity-specific alteration of cortical activity, and excitability, which can outlast the stimulation for some hours (Bindman et al., 1964; Nitsche et al., 2003a; Purpura and McMurtry, 1965). Similar effects are obtained by non-invasive stimulation of the human brain (Nitsche and Paulus, 2000, 2001). The primary mechanism is a subthreshold alteration of the resting membrane potential (Purpura and McMurtry, 1965), whereas the after-effects seem to resemble synaptic plasticity of glutamatergic connections (Liebetanz et al., 2002; Nitsche et al., 2003b, 2004). In most studies, anodal tDCS enhances, while cathodal tDCS reduces cortical excitability, however, some stimulation-intensity, and duration-dependent non-linear effects of the stimulation have been described recently (Batsikadze et al., 2013; Monte–Silva et al., 2013; Nitsche et al., 2008). These effects seem to be localized primarily at the intracortical level (Stagg and Nitsche,

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2011). Neuromodulators, which are involved in a multitude of neuropsychiatric diseases, have a prominent impact on the effects of tDCS on cortical excitability (Nitsche et al., 2012a,b). Beyond regional effects under the stimulation electrodes, tDCS affects functional connectivity. Specifically, it modulates the connections between remote, but functionally associated areas (Polanía et al., 2011a; Polanía et al., 2011b). These features make it an interesting tool to explore, and alter the physiological foundation of psychological and behavioral processes in health and disease. Indeed, especially neuroplasticity-inducing tDCS-protocols have been shown to affect a variety of functions in healthy humans, and patients suffering from neuropsychiatric diseases (Flöel, 2014; Kuo et al., 2014; Kuo and Nitsche, 2012). We will give an overview about these effects, including putative mechanisms, and will discuss future applications as well as recent technical developments, which are important for the use of tDCS in neuropsychological research.

2. tDCS and cognition-studies in healthy humans

2.1. Perception and attention

Perception and attention are elementary cognitive processes, closely connected to external stimuli. Perception can be defined as the organization, interpretation, and integration of sensory stimuli to represent the environment (Schacter, 2012). Attention involves focusing on a specific subset of information, while ignoring interfering stimuli, i.e. the preferential processing of specific types of cognitive information.

tDCS studies exploring perception were performed for visual, somatosensory, auditory and multisensory modalities (Kuo and Nitsche, 2012). For visual perception, Antal et al. (2001) investigated the effect of relatively short-lasting tDCS of the primary visual cortex on perception of static and dynamic contrasts (Antal et al., 2001). Excitability-diminishing cathodal tDCS reduced contrast perception, while anodal tDCS was without effect. Longer anodal stimulation of the same area enhanced contrast sensitivity of central visual regions (Kraft et al., 2010). Differences of the stimulation protocols as well as the more detailed analysis of contrast perception in the second study might have caused the opposing results (Kuo and Nitsche, 2012). For motion perception, the visual area V5 is thought to play a crucial role. Accordingly, in a moving dot paradigm, excitability-enhancing anodal tDCS improved perception, when only coherently moving dots were presented, while excitability-reducing cathodal tDCS improved movement perception when the coherently moving dots were presented among dots moving in random directions, and thus in a noisy environment (Antal et al., 2004a). This shows that the modulatory effect of tDCS on cortical functions can have a different impact on performance depending on task characteristics. In the coherent dot task, further excitability enhancement via anodal tDCS will increase activity of the movement-related representations of the coherent dots, and thus improve performance, while in the noisy task condition including random movements also these representations would be enhanced by excitability-enhancing tDCS, and thus noise will be increased. In the latter condition, excitability-diminishing cathodal tDCS would decrease respective noisy activity, and thus improve performance. For more complex visual precepts, Varga et al. (2007) explored the contribution of the right lateral temporo-parietal cortex to face adaptation. In accordance with the presumed relevance of this area for the perception of faces, excitability-diminishing tDCS over this region, but not the primary visual cortex, reduced face adaptation (Varga et al., 2007).

For auditory perception, Heimrath et al. (2014) investigated the effects of anodal tDCS over left or right auditory cortex (T7 or T8) on the perception of rapidly changing acoustic cues. Anodal tDCS of the left auditory cortex deteriorated performance, in accordance with a left hemispheric dominance for the processing of rapid temporal cues (Heimrath et al., 2014). The performance-diminishing effect of excitability-enhancing anodal tDCS might be caused by a noise-increasing effect of the stimulation, or supra-optimal activity induced by tDCS.

For somatosensory perception, Antal et al. observed a diminishing effect of cathodal tDCS on laser-induced pain in the hand with stimulation applied over the contralateral somatosensory cortex (Antal et al., 2008). In accordance, cathodal tDCS over this area increased pain perception thresholds in another study (Grundmann et al., 2011). Also cathodal tDCS over the left primary motor cortex (M1) increased cold and mechanical detection thresholds as well as mechanical pain thresholds (Bachmann et al., 2010). However, in two other studies only anodal tDCS over M1 reduced pain perception (Ihle et al., 2014; Zandieh et al., 2013).

To evaluate the contribution of temporal areas to multisensory perception, anodal, cathodal and sham tDCS were applied bilaterally over T3 and T4 during a go-no-go task in which stimuli were shapes and non-words. The results show worsened performance for congruent trials in males during cathodal tDCS, but reduced reaction times for incongruent stimuli during anodal and cathodal tDCS, in accordance with a relevant contribution of this area to multisensory integration (Lapenta et al., 2012).

tDCS studies aimed to explore the physiological basis of attention in most cases applied stimulation over areas involved primarily in top-down processing, i.e. the dorsolateral prefrontal (DLPFC) and parietal cortex (PC). Different aspects of attention were investigated, such as alerting, orientation, executive function, internal or external attention, and visual, spatial or multisensory attention.

Tanoue et al. investigated the contribution of the DLPFC and PC to attention in a task suited to discern external cue-driven from working memory-determined attentional processes. Excitability-diminishing cathodal tDCS over both areas reduced performance in both tasks. The effect was largest for prefrontal stimulation and working memory-based information processing (Tanoue et al., 2013). Furthermore, anodal tDCS over the right frontal cortex improved selectively the alerting component of attention in an attention network task (Coffman et al., 2012), and anodal tDCS over the DLPFC enhanced attentional bias acquisition (Clarke et al., 2014). The results of these studies are in accordance with a relevant contribution of the DLPFC to attentional top-down processing.

For the involvement of the posterior parietal cortex (PPC) in visuo-spatial attention, anodal tDCS biased visuo-spatial attention towards the contralateral hemispace, and cathodal tDCS had antagonistic effects (Sparing et al., 2009). Following a related rationale, anodal tDCS over the left PPC reduced visual pseudoneglect in a greyscale task, whereas cathodal and sham stimulation were without effect (Loftus and Nicholls, 2012). The results of these studies are in accordance with a visual attention-directing effect of tDCS over the PPC. Interestingly, only cathodal tDCS with 2 mA improved top down processing, when the intraparietal sulcus was stimulated for modulation of visual attention (Moos et al., 2012). This effect might be caused by an enhancement of the signal-to-noise ratio induced by excitability-diminishing tDCS in this task (Antal et al., 2004b). Alternatively, it cannot be ruled out that similar to primary motor cortex tDCS with 2 mA, cathodal stimulation in this study had an excitability-enhancing effect (Batsikadze et al., 2013), or that orientation of the targeted neurons in the intraparietal sulcus results in an excitability-enhancing effect of cathodal tDCS. Beyond visuo-spatial attention, the supramodal relevance of the PPC for attentional processes was underscored by a performance-enhancing effect of anodal tDCS in a multisensory

Table 1
tDCS studies in healthy humans, Shown are stimulation parameters and effects of tDCS conducted in healthy humans for the main psychological processes explored so far. N=no; Y=Yes,?=not known, electrode positions refer to the International 10 20 EEG system, or to defined cortical areas.

Study	Study design				Stimulation parameters				Electrodes			Task	Effects	Side-effects
	Randomized	Placebo	Blinded	Number of subjects	Current strength (mA)/current density (mA/cm^2)	Duration (min)	Polarity	tDCS timing	Target electrode	Return electrode	Size (active/return) (cm^2)			
Perception														
Antal et al. (2001)	?	N	?	15	1/0.028	7	Anodal and cathodal	Online	Oz	Cz	35/35	Visual contrasts	Static and dynamic contrast sensitivities reduced during and after cathodal tDCS	N
Antal et al. (2004a)	?	N	?	Exp 1: 12 Exp 2: 10	1/0.028	7	Anodal and cathodal	Online	left V5 , Oz or C3	Cz or above contralateral orbit	35/35	MCving dots paradigm	Anodal tDCS improved performance when only coherently moving dots were presented. When coherently and randomly moving dots were presented, cathodal tDCS improved, and anodal tDCS worsened performance	N
Rogalewski et al. (2004)	N	Y	Y	13	1/0.028	7	Anodal and cathodal	Offline	C4	Above contralateral orbit	35/35	Tactile discrimination	Cathodal tDCS decreased tactile perception	N
Varga et al. (2007)	Y	Y	Y	17	1/0.028	10	Anodal and cathodal	Online	Oz or P6-P8	Cz	35/35	Face adaptation	Cathodal tDCS decreased magnitude of face adaptation	N
Ragert et al. (2008)	N	Y	Y	10	1/0.04	20	Anodal	Offline	Left S1	Above contralateral orbit	25/25	Grating orientation	Anodal tDCS enhances tactile spatial acuity	N
Antal et al. (2008)	Y	Y	Y	10	1/0.028	15	Anodal and cathodal	Offline	Left S1	Above contralateral orbit	35/35	Verbal numeric analog score of laser-induced pain	Cathodal tDCS diminished pain perception and the amplitude of laser evoked potentials	N
Kraft et al. (2010)	Y	Y	Y	12	1/0.04	15	Anodal and cathodal	Offline	O1 or O2	Cz	25/70	Visual threshold perimetry	Anodal tDCS enhanced contrast sensitivity	N
Mathys et al.	Y	Y	Y	9	2/0.125	20	Cathodal	Offline	Posterior	Above	16/16	Indidually	Diminished	N

(2010)									superior temporal gyrus (pSTG) and posterior inferior frontal gyrus (pIFG) - left and right	contralateral orbit		optimized pitch matching	accuracy in pitch matching after cathodal stimulation over both areas	
Bachmann et al. (2010)	Y	Y	Y	8	1/0.028	15	Anodal and cathodal	Offline	C3	Above contralateral orbit	35/35	Quantitative sensory testing	Contralateral cathodal tDCS diminished somatosensory perception	N
Grundmann et al. (2011)	Y	Y	Y	12	1/0.028	15	Anodal and cathodal	Offline	Left S1	Above contralateral orbit	35/35	Quantitative sensory testing	Contralateral cathodal tDCS diminished somatosensory perception	N
Ladeira et al (2011)	Y	Y	Y	11	2/0.057	10	Bilateral anodal and cathodal	Online	T3 and T4	right deltoid muscle	35/35	Random gap detection	Anodal tDCS improved and cathodal decreased performance	N
Lapenta et al. (2012)	Y	Y	?	28	1/0.028	14	Bilateral anodal and cathodal	Online (5 min after tDCS onset)	T3 and T4	right deltoid muscle	35/35	Object go-no-go	Cathodal tDCS worsened performance for congruent trials and reduced reaction times for congruent/incongruent trials in males	N
Zandieh et al. (2013)	Y	Y	Y	22	2/0.057	15	Anodal and cathodal	Online (10 min after tDCS onset)	C3	Above contralateral orbit	35/35	Cold pressor test	Anodal tDCS increased pain threshold and tolerance	N
Ihle et al. (2014)	Y	Y	Y	16	1/0.28	15	Anodal and cathodal	Offline	M1 (identified by TMS)	Above contralateral orbit	35/35	Quantitative sensory test	Anodal tDCS reduced pain perception	N
Heimrath et al. (2014)	Y	Y	Y	15	1.5/0.06	> 10	Anodal	Online (10 min after tDCS onset)	T7 or T8	C4 or C3	25/50	Gap detection	Anodal tDCS over the left auditory cortex altered detection thresholds	N
Attention														
Sparing et al. (2009)	Y	Y	Y	20	1/0.057	10	Anodal and cathodal	Offline	P3 or P4	Cz	25/30	Visual detection	Anodal tDCS over PPC biased visuospatial attention towards the contralateral hemispace. Opposite effect after cathodal tDCS	N
Bolognini et al. (2011)	Y	Y	Y	Exp 1: 12 Exp 2: 15	2/0.057	8	Cathodal	Online	T4, P4 or O2	Above contralateral orbit or Cz	35/35	Sound-induced flash illusion	Perceptual 'fission' was increased after anodal tDCS of	N

Table 1 (*continued*)

Study	Study design				Stimulation parameters				Electrodes			Task	Effects	Side-effects
	Randomized	Placebo	Blinded	Number of subjects	Current strength (mA)/current density (mA/cm^2)	Duration (min)	Polarity	tDCS timing	Target electrode	Return electrode	Size (active/return) (cm^2)			
													the temporal cortex, and decreased after anodal tDCS of the occipital cortex	
Coffman et al. (2012)	Y	N	Y	19	0.1 or 2/0.01 or 0.18	30	Anodal	Online	F10	Left upper arm	11/11	Attention networks	Increased alerting with 2 mA anodal tDCS	N
Loftus and Nicholls (2012)	Y	Y	Y	30	1/0.028	20	Anodal and cathodal	Offline	P3 or P4	Cz	35/35	Gray scales	Reduced pseudoneglect following anodal tDCS over the left posterior parietal cortex (PPC)	N
Moos et al. (2012)	N	Y	Y	20	1 or 2/ 0.028 or 0.057	20	Anodal and cathodal	Offline	Horizontal part of the right parietal sulcus	Above contralateral orbit	35/96	Partial report task and eye tracking	Attentional top-down control enhanced by 2 mA cathodal tDCS	N
Nelson et al. (2014)	Y	Y	Y	19	1/0.028	10	Anodal and cathodal	Online	F3 or F4	F3 or F4	35/35	Vigilance task	Improved vigilance by real, but not sham stimulation, for early, and late task phases	N
Tanoue et al. (2013)	Y	Y	Y	24	1.5/0.049	10	Cathodal	Offline	P4 or F4	Contralateral cheek	35/35	Change detection task	Frontal and parietal tDCS worsened performance	N
Clarke et al. (2014)	Y	Y	Y	77	1/0.041	14 to 19	Anodal	Online	F3	Left superior trapezius muscle	24/24	Attention bias modification	Anodal tDCS increased attentional bias acquisition in the targeted direction (towards or away from threat)	N
Working memory														
Fregni et al. (2005)	Y		Y	Y	15	1/0.028	10	Anodal and cathodal	Online (5 min after tDCS onset)	F3 or M1	Above contralateral orbit	35/35	3-Back verbal working memory	Anodal tDCS over the left DLPFC increased accuracy. No effects on reaction time	N
Ohn et al. (2008)	Y		Y	Y	15	1/0.04	30	Anodal	Online (10, 20 and	F3	Above contralateral orbit	25/25	3-Back verbal working memory	Anodal tDCS improved performance	N

								30 min after tDCS onset)					accuracy	
Berryhill et al. (2010)	Y		Y	Y	11	1.5/0.042	10	Anodal and cathodal	Offline	P4	Left cheek	35/35	Object working memory	Cathodal tDCS impaired performance	N
Mulquiney et al. (2011)	?		Y	Y	10	1/0.028	10	Anodal	Offline	Left DLPFC	Above contralateral orbit	35/35	Object n-back	Anodal tDCS improved performance in the 2-back task	N
Teo et al. (2011)	Y		Y	Y	12	1/0.028 or 2/0.057	20	Anodal	Online (during the last 10 min of tDCS)	F3	Above contralateral orbit	35/35	Object 3-back	2 mA anodal tDCS reduced reaction time in the 3-back task	N
Zaehle et al. (2011)	Y		Y	Y	Exp 1: 16 Exp 2: 16	1/0.028	15	Anodal and cathodal	Offline	F3	Left mastoid	35/35	2-Back letter working memory	Improved performance after anodal as compared to cathodal tDCS. Anodal tDCS increased/ cathodal tDCS decreased ERP in the theta and alpha range	N
Heimrath et al. (2012)	Y		Y	Y	12	1/0.028	30	Bilateral anodal and cathodal	Offline	P8/P10	P7/P9	35/35	Visual-spatial working memory	Anodal tDCS over the right parietal lobe decreased, and cathodal tDCS over this area increased WM capacity for stimuli attended in the left hemifield. Right parietal anodal tDCS reduced ERPs for both hemifields, cathodal tDCS reduced ERPs only for stimuli presented in the right hemifield	N
Sandrini et al. (2012)	Y		Y	Y	27	1.5/0.042	13	Bilateral anodal and cathodal	Offline	P3 or P4	P3 or P4	35/35	Object n-back	In the 1-back task, left anodal-right cathodal tDCS worsened performance. In the 2-back task, the result was reversed	N
Hoy et al. (2013)	Y		Y	Y	18	1/0.028 or 2/0.057	20	Anodal	Offline	F3	Above contralateral orbit	35/35	Object n-back	Anodal tDCS improved performance in the	N

Table 1 (*continued*)

Study	Study design				Stimulation parameters				Electrodes			Task	Effects	Side-effects
	Randomized	Placebo	Blinded	Number of subjects	Current strength (mA)/current density (mA/cm^2)	Duration (min)	Polarity	tDCS timing	Target electrode	Return electrode	Size (active/return) (cm^2)			
													2-back task, and induced alterations of theta and alpha activity	
Learning Motor system														
Nitsche et al. (2003c)	Y		Y	Y	80	1/0.028	15	Anodal and cathodal	Online	Fp1, C3, 2 cm anterior and 2 cm to midline, or 5 cm anterior relative to C3	C4, or above contralateral orbit	35/35	Serial reaction time	Anodal tDCS over M1 increased performance	N
Antal et al. (2004b)	?		Y	?	42	1/0.028	10	Anodal and cathodal	Online	Left V5 , left hand motor cortex (TMS hotspot) or Oz	Cz or above the right orbit	35/35	Visuo-motor coordination	Performance increased in the early learning phase during anodal tDCS over left V5 and left hand motor cortex	N
Vines et al. (2008)	Y		Y	Y	13	1/0.07	20	Bilateral anodal and cathodal, and unilateral anodal	Offline	C3 and C4	Above the left orbit	16.3/30	Finger sequence	Bilateral tDCS improved performance more than unilateral tDCS	N
Galea and Celnik (2009)	Y		Y	Y	9	1/0.057	30	Anodal	Online	Left M1 (identified by TMS)	Above contralateral orbit	25/25	Thumb motor training	Anodal tDCS improved motor memories	N
Kang and Paik (2011)	Y		Y	Y	11	2/0.08	20	Anodal and cathodal	Offline	C3 and/or C4	Above contralateral orbit	25/25	12-Digit finger sequence serial reaction time	Uni- and bilateral tDCS improved motor learning	N
Foerster et al. (2013)	Y		Y	Y	18	2/0.1	13	Anodal	Online	Right M1, premotor cortex, sma, cerebellar hemisphere, left DLPFC	Above contralateral orbit or deltoid muscle (cerebellar tDCS)	20/20	Legibility and writing time of a six-words list	Anodal tDCS over M1 and DLPFC enhanced, anodal cerebellar tDCS deteriorated performance	N
Associative verbal														
Flöel et al. (2008)	Y		Y	Y	19	1/0.028	20	Anodal and cathodal	Online	Wernicke´s area (Cp5)	Above contralateral orbit	35/35	Artificial language learning paradigm	Anodal tDCS improved associative verbal learning	N
Elmer et al. (2009)	Y		Y	Y	12	1.5/0.053	5	Anodal and cathodal	Online	F3 or F4	Mastoid	28/100	Verbal memory	Left cathodal tDCS impaired short-term verbal learning	N

Hammer et al. (2011)	Y	Y	Y	Group 1: 18 Group 2: 18	1/0.028	30	Anodal and cathodal	Online (10 min after tDCS onset)	F3	Above contralateral orbit	35/35	Recognition memory	Cathodal tDCS impaired encoding and retrieval after errorful but not errorless learning	N
Perceptual														
Kincses et al. (2004)	Y	?	?	Exp 1: 14 Exp2: 8	1/0.028	10	Anodal and cathodal	Online (5 min after tDCS onset)	Exp 1: Oz Exp 2: Fp3	Cz	35/35	Probabilistic classification learning	Anodal tDCS over Fp3 improved performance	N
Hecht et al. (2010)	Y	Y	Y	Group 1,2: 10 Group 3 (sham): 8	2/0.22	~22	Bilateral anodal and cathodal	Online	F3 and F4	F3 and F4	9/9	Prediction task	With anodal left/ cathodal right tDCS, participants selected the most frequent alternative faster	N
Flöel et al. (2012)	Y	Y	Y	20	1/0.028	20	Anodal	Online	Right temporo-parietal cortex	Above contralateral orbit	35/100	Object-location learning paradigm	Improved recall 1 week after learning only after anodal tDCS	N
Pirulli et al. (2013)	?	Y	?	52	1.5/0.093	online exp: 22 offline exp: 30	Anodal	Online and offline	V1	Right arm	16/60	Visual perception learning	Anodal tDCS induced a larger facilitation in task execution if applied before performance	N
Sehm et al. (2013)	Y	Y	Y	36	1/0.04	20	Anodal	Online	Left inferior frontal or left inferior parietal cortex	Above contralateral orbit	25/25	Degraded speech paradigm	Anodal tDCS over the left inferior frontal gyrus improved learning, tDCS over the inferior parietal cortex introduced a response bias	N
Decision making														
Fecteau et al. (2007)	Y	Y	Y	36	2/0.057	~15	Bilateral anodal and cathodal	Online (5 min after tDCS onset)	F3 or F4	F3 or F4	35/35	Risk task	Right anodal/ left cathodal increased "safe" choice	N
Knoch et al. (2008)	?	Y	Y	64	1.5/0.042	~14	Cathodal	Online (4 min after tDCS onset)	F4	above contralateral orbit	35/100	ultimatum Game	Cathodal tDCS increased acceptance rate of unfair offers	N
Boggio et al. (2010)	Y	Y	Y	28	2/0.057	~15	Bilateral anodal and cathodal	Online (5 min after tDCS onset)	F3 or F4	F3 or F4	35/35	Gambling	Left anodal/ right cathodal stimulation increased choice of high-risk prospects	N

Table 1 (*continued*)

Study	Study design				Stimulation parameters				Electrodes			Task	Effects	Side-effects
	Randomized	Placebo	Blinded	Number of subjects	Current strength (mA)/current density (mA/cm^2)	Duration (min)	Polarity	tDCS timing	Target electrode	Return electrode	Size (active/return) (cm^2)			
Pripfl et al. (2013)	Y		Y	Y	No-smokers: 18 Smokers: 18	0.45/0.085	15	Bilateral anodal and cathodal	Online (5 min after tDCS onset)	F1,F3 and AF1 or F2,F4 and AF2	F3 or F4	5.3/35	Columbia card	Anodal left/cathodal right tDCS decreased risk-taking in the 'cold' cognition task. In the 'hot' version, anodal right/cathodal left tDCS decreased risk-taking in smokers and increased it in non-smokers.	Sleepiness, tingling and itching
Emotion														
Boggio et al. (2008)	Y		Y	Y	14	2/0.057	8	Anodal	Online	T3	T4	35/35	Facial expression go-no-go	Less errors during temporal anodal tDCS in females responding to sad faces	N
Peña-Gómez et al. (2011)	Y		Y	Y	16	1/0.028	20	Anodal and cathodal	Online (5 min after tDCS onset)	F3	C4	35/35	Emotional processing	Anodal tDCS reduced emotional valence for negative stimuli	N
Nitsche et al. (2012)	Y		Y	Y	Exp 1: 14 Exp 2: 17	1/0.028	Exp 1: 20 Exp 2: 10	Anodal and Cathodal	Exp 1: offline Exp 2: online	F3	Above contralateral orbit	35/35	Emotional face recognition	Left DLPFC tDCS improved emotional face recognition	N
Vanderhasselt et al. (2013)	N		Y	Y	25	2/0.057	20	Anodal	Offline	F3	Above contralateral orbit	35/35	Cued emotional control	Enhanced cognitive control for positive relative to negative information	Transient headache, skin itching and redness

Table 2
tDCS studies in patients, Shown are stimulation parameters and effects of tDCS conducted in patients suffering from selected neurological/psychiatric diseases with regard to cognitive processes. N = no; Y = Yes,? = not known, n.a. not available, electrode positions refer to the International 10 20 EEG system, or to defined cortical areas.

Study	Study design				Stimulation parameters					Electrodes			Combined intervention	Task	Effects	Side-effects
	Randomized	Placebo	Blinded	Number of subjects	Current strength (mA)/current density (mA/cm^2)	Duration /session (min)	sessions	Polarity	tDCS timing	Target electrode	Return electrode	Size (active/ reference) (cm^2)				
Depression																
Boggio et al. (2007a)	Y		Y	Y (Double)	26	2/0.06	20	10 (10 days)	Anodal	Before the task, first 9 sessions without task performance	Anodal: left DLPFC or OZ (V1)	Above contralateral orbit	35/35	–	Affective go-no-go task	Anodal stimulation of the left DLPFC significantly improved affective go-no-go task performance	Mild transient headache, itching sensation
Loo et al. (2012)	Y		Y	Y (Double)	64	2/0.06	20	15 (3 weeks)	Anodal	Before the task, first 14 sessions without task performance	Anodal: left DLPFC	Above contralateral orbit	35/35	–	Symbol digit modalities Test	Attention and working memory improved after active but not sham tDCS	Transient hypomania, skin redness, itching etc.
Oliveira et al. (2013)	Y		Y	Y (Double)	28	2/0.08	30	1	Anodal	Online	Anodal: left DLPFC, cathodal: right DLPFC	n,a.	25/25	–	n-back task	Improved working memory	N
Brunoni et al. (2013)	Y		Y	Y (Double)	28	2/0.08	30	1	Anodal	Online	Anodal: left DLPFC, cathodal: right DLPFC	n,a.	25/25	–	Probabilistic classification learning task	tDCS prevented implicit learning as compared to sham tDCS	Not reported
Wolkenstein and Plewnia (2013)	Y		Y	Y (Double)	22	1/0.03	20	1	Anodal	Online	Anodal: left DLPFC	Cathodal: right deltoid muscle	35/35	–	Delayed response working memory task	Eworking memory performance, abolished attentional bias	N
Brunoni et al. (2014a)	Y		Y	Y (Double)	37	2/0.08	30	10	Anodal	Online	Anodal: left DLPFC cathodal: right DLPFC	n.a.	25/25	Computer-based CCT (mPASAT)	Paced Auditory Serial Addition Task (PASAT)	tDCS augmented the clinical effects of cognitive control therapy (CCT) in older individuals	N
Segrave et al. (2014)	Y		Y	Y (Double)	27	2/0.06	24	5	Anodal	Online	Anodal: left DLPFC	Cathodal: above contralateral orbit	35/35	CCT (modified Wells Attentional Training and adaptive Paced Serial Addition Task)	Affective and non-affective versions of the two-back working memory task	Combination therapy resulted in more accurate performance than tDCS alone or CCT with sham stimulation at the early treatment period	Not reported
Brunoni et al.	Y		Y	Y	24	2/0.08	30	10	Anodal	Online	Anodal: left	n,a.	25/25	–	Word	Active	Not reported

Table 2 (*continued*)

Study	Study design				Stimulation parameters					Electrodes			Combined intervention	Task	Effects	Side-effects
	Randomized	Placebo	Blinded	Number of subjects	Current strength (mA)/current density (mA/cm^2)	Duration /session (min)	sessions	Polarity	tDCS timing	Target electrode	Return electrode	Size (active/ reference) (cm^2)				
(2014b)			(Double)							DLPFC cathodal: right DLPFC				emotional stroop Task	bifrontal tDCS but not sham modified negative attentional bias	
Schizophrenia																
Vercammen et al. (2011)	Y		Y	20	2/0.06	20	1	Anodal	Online	Anodal: left DLPFC	Above contralateral orbit	35/35	–	Weather prediction test (probabilistic association learning)	improved performance in a subset of patients, who were able to learn the task at baseline	Not reported
Ribolsi et al. (2013)	Y		Y	Not report	15	1/0.03	10	1	Anodal	Online	Anodal electrodes: right PPC and left PPC	Cathodal: contralateral shoulder	35/35	–	Line bisection (LB), mental number line (MNL)	A systematic rightward bias for LB was partially corrected by selective right posterior parietal tDCS	Not reported
Göder et al. (2013)	Y		Y	Y (Double)	14	0–300 μA, 0.75 Hz	25 (5 blocks of 5 min)	1	Anodal	Offline, 10 min after subjects entered stage 2 sleep	Anodal electrodes: left DLPFC and right DLPFC	Cathodal: contralateral shoulder	8/8/8	–	Rey auditory–verbal learning test, mirror-tracing skills	Greater retention of verbal material together with a more positive mood the following morning	N
Hoy et al. (2014)	Y		Y	Y (Double)	18	1/0.03, 2/0.06	20	1	Anodal	Offline	Anodal: left DLPFC	Above contralateral orbit	35/35	–	2-back working memory task	Significant improvement following 2 mA stimulation only	N
Alzheimer's dementia																
Ferrucci et al. (2008)	Y		Y	Y (Double)	10	1.5/0.06	15	1	Anodal and cathodal	Offline	Bilateral temporo-parietal area (left P3-T5 and right P6-T4)	Right deltoid muscle	25/25	–	Word recognition task (WRT), visual attention task (VAT)	After anodal tDCS, accuracy of WRT increased whereas after cathodal tDCS it decreased	N
Boggio et al. (2009)	Y		Y	Y (Double)	10	2/0.06	30	1	Anodal	Online	Left DLPFC or left temporal cortex	Above contralateral orbit	35/35	–	Stroop, Digit Span, Visual Recognition Memory task (VRM)	Significant improvement of VRM after temporal ($p=0.01$) and prefrontal tDCS as compared with sham	N

															stimulation	
Boggio et al. (2012)	Y	Y	Y (Double)	15	2/0.06	30	5 (5 days)	Anodal	Offline	Bilateral temporal lobes	Right deltoid muscle	35/35	–	MMSE, ADAS-Cog, Visual Recognition Task (VRT), Visual Attention Task (VAT)	VRM performance improved	N
Cotelli et al. (2014)	Y	N	Y (Double)	36	2/0.08	25	10 (10 days)	Anodal	Combined therapy without task performance	Left DLPFC	Right deltoid muscle	25/60	Individualized computerized (IC) memory training	Face-Name Association memoryTask (FNAT)	IC memory training group with/without anodal tDCS showed improved FNAT performance compared with motor training with anodal tDCS	Not reported
Mild cognitive impairment																
Meinzer et al. (in press)	Y	Y	Y (Double)	18	1/0.03	20	1	Anodal	Online	Left ventral IFG	Above contralateral orbit	35/35	–	Semantic word-retrieval task	Anodal-tDCS significantly improved semantic word-retrieval performance and reduced task-related prefrontal hyperactivity	Not reported

field exploration task (Bolognini et al., 2011).

Taken together, tDCS is suited to modulate perception and attention in various domains, and thus can contribute to our understanding of underlying physiology. Hereby, it is important to realize that excitability enhancement is not linearly connected to improvement, and excitability diminution to worsening of performance, but that task characteristics such as noise play an important role. Studies including active control conditions moreover show that the effects on perception and attention are relatively localized, in at least partial contrast to the rather unspecific physical effects suggested by some modeling studies (for a more detailed discussion see below). The majority of studies were designed to deliver information about the contribution of specific brain areas to performance, and thus the relatively limited effect size obtained in most studies should not be seen as problematic.

2.2. Working memory

Working memory (WM) provides temporary storage and manipulation of information necessary for complex brain functions, such as cognitive tasks, language comprehension, learning, and reasoning. The prefrontal cortex is a relevant part of a distributed network of interconnected brain areas involved in WM. These include furthermore the parietal and temporal association areas of the cerebral cortex, cingulate and limbic areas, and subcortical structures such as the mediodorsal thalamus and the basal ganglia (Constantinidis and Procyk, 2004; Gazzaley et al., 2004).

Fregni et al. applied anodal, cathodal or sham stimulation over the left DLPFC during performance of a 3-back letter WM task in healthy participants (Fregni et al., 2005). Anodal tDCS caused a significant accuracy improvement. Also anodal tDCS applied before performance over the left DLPFC enhanced performance in a 2-back task, compared with cathodal tDCS (Zaehle et al., 2011). The EEG results obtained in this study suggest that tDCS altered WM performance by modulating oscillatory brain activity in the theta and alpha frequency bands, which were increased by anodal tDCS, but reduced via cathodal stimulation. These results were largely replicated by another study (Hoy et al., 2013), which explored the impact of different stimulation intensities on performance in a 2- and 3-back task. Interestingly, in this study only anodal tDCS with 1 mA intensity improved performance in the 2-back task. Alterations of theta and alpha activity only took place for this stimulation condition. The impact of the posterior parietal cortex on working memory performance was explored in one study for the n-back task so far. Here, bilateral parietal tDCS performed before task performance had discernable effects on reaction times in the 1- and 2-back task. In the 1-back task, left anodal-right cathodal tDCS worsened performance as compared to sham tDCS and the antagonistic electrode arrangement, whereas in the 2-back task a reversed result was obtained (Sandrini et al., 2012). The authors interpret the results as a hint for different processing strategies dependent on task difficulty. A couple of other studies used a methodological design similar to the studies mentioned above, with similar outcomes (Table 1).

Apart from verbal working memory, Heimrath et al. (2012) investigated the impact of bilateral parietal tDCS on performance in a visuo-spatial WM task. Participants performed a delayed matching-to-sample WM task. Right parietal cathodal combined with left parietal anodal tDCS increased WM capacity for stimuli in the left hemifield, while antagonistic tDCS converted the effects. Both stimulation protocols reduced performance of stimuli presented in the right hemifield. In accordance, right parietal anodal tDCS reduced the amplitudes of event-related potentials (ERP) for both hemifields, whereas right parietal cathodal tDCS reduced it only for stimuli presented in the right hemifield (Heimrath et al., 2012). One important aspect explaining behavioral and ERP data might be that stimulation duration was 30 min, and a similar stimulation duration of anodal tDCS over the motor cortex induces an excitability reduction (Monte–Silva et al., 2013). The physiological effects of cathodal tDCS for such a long stimulation duration are unknown, however an excitability-enhancing effect of intensified cathodal tDCS has been described recently (Batsikadze et al., 2013). Thus it might be that cathodal and anodal tDCS resulted in reversed physiological effects in this study.

These studies deliver clear evidence that prefrontal and parietal task-related activity alterations are causally related to performance. Furthermore, respective performance alterations are associated with specific effects on EEG, and ERP parameters, which underline the strong connections between physiology, and cognition (Table 2).

2.3. Learning

Given that one of the major effects of tDCS is the induction of long-term potentiaton (LTP), and depression (LTD)-like plasticity, which are thought to be the physiological basis of learning and memory processes, using tDCS to modulate these cognitive processes is an attractive idea. Indeed, numerous studies have been conducted in this field.

For motor learning, relevantly involved cortical structures are the primary motor cortex (M1, Muellbacher et al., 2002; Plautz et al., 2000), pre-motor cortex, supplementary motor area (sma) and parietal association areas. Nitsche et al. investigated the effects of tDCS on sequence motor learning. Anodal and cathodal tDCS were applied to different regions contralaterally to the performing hand: M1, pre-motor, and pre-frontal cortices. Participants receiving anodal tDCS over M1, but not over other areas, showed improved performance (Nitsche et al., 2003c). Other studies report similar effects of anodal tDCS over M1 on motor training (Antal et al., 2004b; Foerster et al., 2013; Galea and Celnik, 2009; Kang and Paik, 2011; Vines et al., 2008). The performance-improving effects of motor cortex tDCS can be long-lasting. Repetitive tDCS over 5 consecutive days during a motor learning protocol resulted in improved performance lasting for at least 3 months after training (Reis et al., 2009). With regard to specific aspects of stimulation protocols, it was shown that also bilateral tDCS improves motor learning (Kang and Paik, 2011; Vines et al., 2008), that increased tDCS intensity might result in better effects (Cuypers et al., 2013), and that stimulation during learning might be critical to improve motor learning (Stagg et al., 2011). Furthermore, it was demonstrated that also stimulation of other areas improves motor learning, that stimulation during task-related activity of the respective area is relevant, and that tDCS over different areas might be relevant for specific aspects of performance. Thus premotor anodal tDCS not during the early learning phase, but during consolidation processes, in which this area is involved, improved performance in the above-mentioned sequence learning task (Nitsche et al., 2010). Cerebellar tDCS improved initial motor learning, but M1 stimulation retention in another study (Galea et al., 2011), and left DLPFC stimulation enhanced the motor learning-improving effects of mental practice (Foerster et al., 2013).

Beyond motor learning, the impact of tDCS on some other learning procedures has been explored. For associative verbal learning, selectively anodal tDCS over the left perisylvian area improved performance (Flöel et al., 2008). In contrast, learning of verbal material was impaired by cathodal tDCS of the left dorsolateral prefrontal cortex (Elmer et al., 2009; Hammer et al., 2011). Improved artificial grammar learning was accomplished via anodal tDCS over Broca's area as compared to sham stimulation or real tDCS over a brain area unrelated to language processing (De Vries et al., 2010).

For perceptual learning, interestingly, anodal tDCS of the primary visual cortex resulted in larger effects when applied before as compared to during task performance (Pirulli et al., 2013). tDCS might also be suited to disentangle the role of involved cortical areas in different components of perceptual learning, because anodal tDCS over the left inferior frontal gyrus improved perceptual learning in a degraded speech paradigm, whereas stimulation over the inferior parietal cortex introduced a response bias (Sehm et al., 2013).

Finally, anodal tDCS of the right temporo-parietal cortex was shown to improve spatial learning (Flöel et al., 2012), and probabilistic learning was improved by left prefrontal stimulation (Hecht et al., 2010; Kincses et al., 2004).

Especially anodal tDCS, which induces LTP-like plasticity, has a relatively uniform learning-enhancing effect, when applied over critical areas. These results demonstrate the relevant role of LTP in learning processes. Additional to these general effects, tDCS seems to be suited to disentangle specific functions of areas in learning and memory formation. The effects can be long-lasting, and titrating of stimulation parameters can improve results, which is encouraging with regard to the development of protocols for future therapeutic application.

2.4. Decision-making

Decision-making is a cognitive process resulting in the selection of a belief or a course of action among several alternative possibilities. Considering the relevance of the DLPFC for decision-making (Krawczyk, 2012; Weber et al., 2004), several tDCS studies investigated the hemispheric balance between right and left DLPFC. Bipolar bihemispheric tDCS over right and left DLPFC was most often applied.

Fecteau et al. (2007) applied online bi-hemispheric tDCS over the left and right DLFPC during performance of a risk decision task. Under right anodal/left cathodal stimulation, participants chose more often the safe prospect compared with the other groups, in accordance with an involvement of the right DLPFC in risk control (Fecteau et al., 2007). Accordingly, in a decision task involving social aspects, the ultimatum game, where a decision has to be made to accept a fair or unfair offer of sharing money between two participants, cathodal tDCS over the right dorsolateral prefrontal cortex did not alter the subjective impression of the fairness of the offer, but resulted in higher acceptance rates also of unfair offers, which can be interpreted as choosing the “safer” alternative (Knoch et al., 2008). Pripfl et al. (2013) however showed that *left* DLPFC anodal tDCS might be also suited to reduce risk-taking under certain conditions dependent on the involvement of emotional contribution (Pripfl et al., 2013).

With regard to parameters affecting decision making, age (Fein et al., 2007; Reed et al., 2008), and substances (i.e. nicotine), beyond others, are relevant factors. Interestingly, the impact of tDCS on decision making seems also to be affected by these parameters. Boggio et al. (2010) found antagonistic effects of tDCS on the risk task introduced by Fecteau et al. (2007) in old participants. Pripfl and co-workers (2013) describe antagonistic effects of prefrontal tDCS on risky decisions involving emotions in smokers and non-smokers, and explain this by inter-group pre-stimulation differences regarding risk-aversion, and risk-seeking impulsivity.

These studies show a relevant contribution of prefrontal areas to decision-making processes. They suggest also that a dedication of certain areas to more/less risky behavior might be an over-simplification, and that the specific effect of tDCS on performance is determined by various parameters, such as emotion, age, and addiction/pharmacological conditions.

2.5. Emotion

Emotions are thought to be related to activity in brain areas that direct attention, motivate behavior, and determine the significance of environmental stimuli. As such, numerous brain areas are involved in emotional processing, relevantly extending the “limbic system”, which was classically assumed to be an anatomical substrate of emotion (Lindquist et al., 2012).

Only a few studies have explored the impact of specific cortical areas on emotional processes via tDCS. Most of these studies evaluated the impact of stimulation on perception of emotional facial expressions, which is critical for understanding the emotional state of others and plays a key role in social interaction (Winston et al., 2002).

Acute emotional changes and emotional face identification were evaluated during and after anodal, cathodal and sham tDCS over the left DLPFC, combined with antagonistic stimulation of the right frontopolar cortex (Nitsche et al., 2012a). Subjective emotions were not influenced, however emotional face identification was subtly improved by tDCS. In principal accordance with an impact of this area on information processing of emotional content, it was shown that anodal tDCS over the left DLPFC decreased the emotional valence for emotionally negative stimuli (Peña–Gómez et al., 2011), and improved cognitive control over emotionally positive stimuli, which was associated with enhanced size of respective ERP amplitudes (Vanderhasselt et al., 2013).

Beyond the contribution of the prefrontal cortex to emotion processing, Boggio et al. (2008) investigated the effects of tDCS applied over the superior temporal cortex on perception of emotional facial expressions (Boggio et al., 2008). This area has been considered as a crucial region in facial expression and threat-related information processing (Tseng et al., 2014). Simultaneous anodal tDCS of the left and cathodal tDCS over the right superior temporal cortex resulted in impaired recognition of sad faces in males, but antagonistic effects in females. Beyond support for the hypothesis of a relevant contribution of this area, these results are in favor for sex-specific hemispherical differences of emotion processing (Lee et al., 2002; Proverbio et al., 2006).

Processing of emotional material can be modulated via prefrontal and temporal tDCS. The results also suggest that the dorsolateral prefrontal cortex is not relevantly involved in emotion generation. Similar to other complex cognitive functions, individual parameters such as sex seem to have a relevant impact on the results, however respective mechanisms are incompletely understood at present. *Generation* of emotions via tDCS might be not an easily achieved aim, because areas involved in these processes are situated relatively far from the cortical surface, and might be difficult to affect by this stimulation technique.

3. Alteration of cognitive functions in patients suffering from neurological and psychiatric diseases

3.1. Depression

Major depressive disorder (MDD) is one of the most pressing public health problems in the world that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, poor concentration, and cognitive impairment (Hall et al., 2011; Mowla et al., 2008). Main pathophysiological features of MDD are an imbalance of left and right prefrontal cortex activation and dysfunctional cortical-subcortical neural networks. Hypoactivity of the left dorsolateral prefrontal cortex (DLPFC) and hyperactivity of subcortical and limbic regions are key features in MDD (Fitzgerald et al., 2008). Abnormalities of functional coupling between

cognition-related regions, particularly prefrontal and anterior cingulate areas, cause cognitive impairment (Vasic et al., 2009). These findings are related to deficits of LTP-like neuroplasticity such as the reduction of synaptic plasticity in a dorsal executive network (Nissen et al., 2010).

Therefore, improvement of imbalanced cortical-subcortical activity and enhancement of LTP-like plasticity may be a way to treat depression including the improvement of cognitive functions. Plasticity induction via tDCS might thus be suited to reduce cognitive and affective symptoms in depression, similar to its effects in healthy humans.

In accordance to its general clinical effects, a couple of studies have shown that prefrontal tDCS in MDD is able to improve cognitive functions, and emotion-related information processing. Loo et al. demonstrated positive cognitive effects of prefrontal tDCS conducted over 3 weeks in MDD (Loo et al., 2012). Beyond positive effects on clinical symptoms, attention and working memory evaluated via the Symbol Digit Modalities Test improved after a single session of active, but not sham tDCS. These results are in accordance with a study in which left DLPFC anodal tDCS improved working memory performance in the n-back task (Oliveira et al., 2013). Working memory and attentional bias also improved by tDCS conducted via an cephalic-extracephalic electrode montage (Wolkenstein and Plewnia, 2013). These authors chose an extracephalic cathode location to make sure that effects could be traced back exclusively to anodal stimulation of the left DLPFC. These results are in accordance with those obtained in healthy humans.

On the other hand, bifrontal tDCS over the DLPFC prevented implicit learning in MDD patients (Brunoni et al., 2013). These results are partially different to those obtained in a previous study conducted in healthy subjects, where left frontopolar anodal tDCS improved performance in this task (Kincses et al., 2004). Although the specific difference of study results might be caused by a multitude of factors, such as different electrode positions, current flow direction, and subject groups, they nevertheless point to the fact that tDCS does not necessarily improve functions, but can have also deleterious cognitive effects under certain conditions.

With regard to emotion-related information processing, Boggio et al. report a positive effect of left anodal DLPFC tDCS on affective control in MDD (Boggio et al., 2007a). More recently, Brunoni et al. reported that bifrontal tDCS significantly modifies negative attentional bias, abolishing slower RT for negative words (Brunoni et al., 2014) in MDD. These reports support the usage of tDCS for the management of affective symptoms in patients with MDD.

Given the fact that prefrontal tDCS improves depressive symptoms, and modifies cognitive processes, also those involving emotional content, combination of tDCS with cognition-altering psychotherapy might be a promising approach. Two recently conducted studies have probed a combination of cognitive control therapy (CCT) and tDCS for the treatment of depression (Brunoni et al., 2014; Segrave et al., 2014). Brunoni et al. used a modified version of the Paced Auditory Serial Addition Task (PASAT) for computer-based working memory exercises for CCT. CCT was delivered in the last 15 min of each active/sham tDCS session (anode over the left, cathode over right DLPFC). Both CCT alone and combined with tDCS significantly improved depressive symptoms after the acute treatment period and at 2 and 4 weeks follow-up. In addition, tDCS augmented the clinical effects of CCT in older individuals, particularly in those displaying improved cognitive performance throughout the trial. This study showed that tDCS can enhance the efficacy of CCT in patient subgroups. Another recently published study shows that only CCT combined with tDCS, but not tDCS alone or CCT alone, resulted in sustained antidepressant response at a 3 weeks follow up after cessation of treatment (Segrave et al., 2014). In this study, CCT was conducted via a modified Wells Attentional Training (8 min, no breaks) protocol and an adaptive Paced Serial Addition Task. These new approaches present a conceptually promising new direction for future research and development of neuromodulation therapy in MDD.

In most available studies aiming for therapeutic effects of tDCS in MDD, however, tDCS was not combined with specific psychotherapeutic approaches, but alone, or combined with pharmacotherapy. A recently conducted systematic meta-analysis conducted for these studies showed that active tDCS was significantly superior for all outcomes in the patients with MDD ($g=0.37$; 95% CI 0.04–0.7; ORs for response and remission were, respectively, 1.63; 95% CI = 1.26–2.12 and 2.50; 95% CI = 1.26–2.49) (Shiozawa et al., 2014). In contrast, Berlim et al. report no significant effects of tDCS on depression in their meta-analysis (Berlim et al., 2013). Several methodological differences between these two reports might explain the different outcomes. To date 27 clinical trials of depression treatment using tDCS are registered at *CkinicalTrials.gov*, reflecting the need for designing protocols with enhanced efficacy.

The results suggest beneficial effects of prefrontal tDCS aimed to re-establish compromised excitability not only on clinical symptoms of patients suffering from MDD, but also on cognitive and cognitive-affective processes. The direction of effects, which is improved performance, and reduced clinical symptoms induced by left dorsolateral prefrontal tDCS, matches that of rTMS for depression treatment (Berlim et al., 2013; Tortella et al., 2014). Conceptually, the combination of tDCS with psychotherapeutic approaches like cognitive control therapy holds promise for future therapeutic approaches, here tDCS might have a gating function for altered information processing of emotion-related content.

3.2. Schizophrenia

Schizophrenia is characterized by thought disturbances, abnormal social behavior, and failures in perception of reality. The symptoms of schizophrenia are caused by abnormal functions of various brain regions. Positive symptoms such as hallucinations are closely related to increased activation of the lateral, medial and anterior temporal cortex (Shergill et al., 2003; Whalley et al., 2007). Behavioral and cognitive dysfunctions are correlated with prefrontal hypofunction (Enomoto et al., 2011; Larquet et al., 2010). Counteracting the respective pathological alterations of cortical activity via tDCS might thus be a promising therapeutic approach.

Several studies suggest an impact of tDCS on cognitive functions in schizophrenia. Hoy et al. investigated the effect of tDCS-dose on working memory performance (Hoy et al., 2014). Anodal stimulation was delivered in three conditions (1 mA, 2 mA, and sham) for 20 min over the left DLPFC. Only 2 mA tDCS enhanced performance in the 2-back working memory task. For probabilistic association learning, anodal tDCS over the left DLPFC combined with cathodal tDCS over the right frontopolar region failed to improve performance with regard to whole sample performance (Vercammen et al., 2011), but improved it in a subset of patients, who were able to learn the task at baseline. Ribolsi et al. conducted anodal tDCS over the posterior parietal cortex (PPC) for enhancing visuospatial perception (Ribolsi et al., 2013). They applied stimulation over the right and left PPC in 2 different sessions. This study used the line bisection (LB) and mental number line bisection (MNL) task for assessing visuospatial perception, especially perceptual pseudoneglect in schizophrenia. The patients showed a systematic rightward bias on LB in comparison with healthy subjects, which was partially corrected by right posterior parietal tDCS. Finally, Göder and coworkers report that sinusoidal tDCS (anode bilaterally over frontolateral locations; cathode over the

mastoids) during sleep in patients with schizophrenia resulted in greater retention of verbal material together with a more positive mood the following morning compared with sham stimulation (Göder et al., 2013).

The number of clinical trials aiming to reduce the severity of this disease via tDCS is relatively small. In a recently published randomized, double-blind controlled trial, auditory verbal hallucinations in 30 patients with schizophrenia were robustly reduced by tDCS relative to sham stimulation for up to three months. Moreover, stimulation resulted in a reduction of negative symptoms (Brunelin et al., 2012). In this study, a bipolar stimulation montage (anode on left DLPFC, cathode on left temporoparietal cortex, (TPC)) was applied to counteract left temporoparietal hyperactivity, and left DLPFC hypoactivity. In this study, tDCS moreover improved insight. To date, 16 clinical trials of schizophrenia treatment using tDCS are registered at *ClinicalTrials.gov.*

The results of these initial studies suggest a positive effect of tDCS on cognitive and behavioral dysfunctions in schizophrenia. In accordance, tDCS improved clinical symptoms related to cognitive dysfunctions, but also hallucinations. Especially with regard to cognitive symptoms, which are usually not addressed by pharmacological therapy, tDCS might evolve as an interesting adjunctive therapy in future.

3.3. Alzheimer's disease and its precursors

Alzheimer's disease (AD) is the most common cause of dementia (60–70% of cases) and affects memory, executive function, attention, perception, learning capacity, and language (Reitz et al. 2011). Both cholinergic and glutamatergic mechanisms play an important role (Francis, 2005). In addition, abnormal accumulation of neurofibrillary tangles and amyloid beta-protein is causally related to AD (McKee et al., 1991; Perl, 2010). Brain atrophy related to neuronal destruction results in hypo-activity of various cortical regions (Desgranges et al., 1998; Perani et al., 1993; Salmon et al., 2000). McDonald and coworkers demonstrated that regional brain atrophy is closely related to domain-specific cognitive decline (McDonald et al., 2012). Mild cognitive impairment (MCI) resembles objective cognitive decline, which is however not severe enough to require help in activities of daily living. Etiologically, this is a heterogeneous diagnosis, which however converts from 5-20% to dementia per year (Langa and Levine, 2014).

tDCS is suited to modulate activation of cortical areas, and has been shown accordingly to improve cognitive functions in healthy humans. Thus it was hypothesized that cognitive functions could be improved also in AD with this stimulation approach. Ferrucci and coworkers investigated the effects tDCS over the temporoparietal cortex on recognition memory and visual attention in patients with AD (Ferrucci et al., 2008). In this study, anodal tDCS significantly improved word recognition memory, while cathodal tDCS worsened it, and sham stimulation had no effect. Boggio et al. conducted a study in which the effects of anodal or sham tDCs over the DLPFC and temporal cortex on attention (Stroop task), working memory (Digit Span) and a Visual Recognition Memory task (VRM) was explored in AD (Boggio et al., 2009). VRM performance after left temporal cortex and left DLPFC stimulation was significantly enhanced in comparison with sham stimulation, respectively, whereas stroop test and digit span performance were not affected.

In another group of studies, repeated stimulation approaches were developed to explore if tDCS can result in longer-lasting and possibly clinically meaningful effects on cognitive processes. Boggio et al. applied bilateral anodal tDCS during 5 consecutive days over the temporal lobes in AD. As for single session stimulation, tDCS significantly improved visual recognition memory, and this improvement persisted for at least 4 weeks after intervention (Boggio et al., 2012). In another clinical trial, which combined tDCS with a computerized Face-Name Association memory Task (FNAT) training in patients with AD, two weeks active tDCS combined with memory training was however not superior to placebo tDCS-combined FNAT training (Cotelli et al., 2014).

For MCI, Meinzer et al. applied anodal tDCS to the left inferior frontal cortex during task-related and resting-state fMRI (Meinzer et al., in press). Anodal tDCS significantly improved semantic word retrieval to the level of controls, reduced task-related prefrontal hyperactivity, and resulted in normalization of abnormal network configuration during resting-state fMRI. To date 17 clinical trials of AD and MCI treatment using tDCS are registered at *ClinicalTrials.gov.*

The results of the available studies suggest a future therapeutic potential of tDCS in AD and MCI. Given the relatively minor neurodegenerative change, tDCS in MCI might be more promising than stimulation in AD. Since clinical results are partially heterogeneous, shaping of stimulation protocols would be relevant to reveal the full clinical potential of tDCS in this application. Here combination of stimulation with cognitive training might be a promising approach.

4. Strategies for tDCS application in neuropsychology

tDCS has been increasingly applied in the last years in humans especially with regard to three main fields: exploration of the physiological characteristics of plasticity, the physiological basis of psychological and behavioral processes, and for clinical applications. Although promising results have been reported in many studies (for overviews see Flöel, 2014; Kuo et al., 2014; Kuo and Nitsche, 2012; Nitsche and Paulus, 2011; Stagg and Nitsche 2011), currently available protocols suffer from some potential shortcomings, which have to be addressed to improve the interpretability of findings and the efficacy of stimulation.

It is well known that tDCS at an intensity of 1 mA on the human motor cortex with an electrode size of 35 cm^2 induces polarity-specific alterations on cortical excitability during and after stimulation. The "classic" assumption is that anodal tDCS enhances cortical excitability, and cathodal tDCS diminishes it, and that enhanced stimulation intensity, and duration increase efficacy of tDCS. Whereas these results have been described in numerous studies (for an overview see Nitsche et al., 2003a, 2008; Nitsche and Paulus, 2011), it should be kept in mind that these were obtained in healthy young humans in the model of the primary motor cortex. Increased stimulation duration, and intensity does not in all cases increase effects, if certain limits are exceeded (Batsikadze et al., 2013; Monte–Silva et al., 2013). Finally, transferability of the results to other cortical areas, and patients suffering from neuropsychiatric diseases, most of them additionally under medication, has not been shown in each case. Since the effects of tDCS might be relevantly affected by cortical baseline activity, and excitability, as well as availability of neuromodulators, which differ between cortical regions, and are often altered in neuropsychiatric diseases, respective studies are required.

In the "classic protocols", moreover, stimulation is delivered via relatively large electrodes, which do not allow a very focal stimulation. While this might not be a major problem for clinical treatment, where in some cases "unfocal" stimulation might be superior because of effects on a larger cortical area, for cognitive studies aimed to explore physiological mechanisms a more focal stimulation would be advantageous. It might be possible to achieve more focal stimulation by smaller electrodes, or new arrangements (Edwards et al., 2013; Nitsche et al., 2007; Ruffini, Fox et al., 2014), although the physiological effects of these new

protocols have not been tested in each case.

With regard to the interaction of stimulation with cognition/clinical symptoms, the sometimes made implicit assumption that anodal tDCS enhances excitability and is beneficial, and cathodal tDCS reduces function because of its excitability-diminishing effect, is a simplification, which has been proven already to be wrong (Antal et al., 2004a; Weiss and Lavidor, 2012). Similarly, it should not been taken for granted that the physiologically "best" stimulation protocol always results in the best effects, because stimulation and cognition might interact in a non-linear fashion (Kuo et al., 2008). Therefore, more studies exploring the complex interaction between cognition, and stimulation are needed.

Finally, the physiological, psychological/behavioral and clinical effects of tDCS are subject to interindividual variability (López–Alonso et al., 2014; Wiethoff et al., 2014). While variability is not restricted to tDCS, but inherent to all non-invasive brain stimulation protocols, it would nevertheless be important to identify sources of variability, and develop strategies to circumvent this problem.

In the remaining paragraphs, we will discuss these topics into larger detail.

4.1. Parameters of tDCS treatment; intensity and dosage of stimulation

Optimal tDCS parameters should result in stimulation protocols inducing adequate and effective neural facilitation/inhibition of the respective target areas without relevant side effects. The total amount of electrical stimulation delivered to the brain is determined by the following parameters: stimulation intensity, stimulation duration, interval between stimulations, accumulative stimulation time, size of electrodes, distance of electrodes and electrode montage. In addition, disturbances of brain architecture, CNS-acting medication, age, and other factors might have an impact on stimulation effects.

In particular, stimulation intensity and duration are assumed to be basic parameters and 1.0–2.0 mA (electrode size between 25 and 35 cm^2) for 15–40 min were mainly applied in the previous reports. For the motor cortex of healthy adult subjects, a positive linear relationship between intensity (up to 1 mA), duration (up to 13 min), and physiological effects was described (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003d). However, in case of high intensity (e.g. 2.0 mA) and long duration stimulation ($\geq$20 min), non-linear, partially reversed effects of tDCS are accomplished (Batsikadze et al., 2013; Monte–Silva et al., 2013). Apart from motor cortex stimulation of healthy subjects, many studies aimed to reduce symptoms, and improve psychological functions in patients, applied stronger, and longer-lasting stimulation with good effects (Boggio et al., 2012, 2009; Brunoni et al., 2014a; Oliveira et al., 2013), which might be explained by different cortical areas stimulated or different baseline activity of the stimulated area due to the disease or medication. For rational application of tDCS, including an improved understanding of the physiological foundation of its modulatory impact on cognition, however it would be relevant to explore systematically the physiological impact of specific tDCS protocols on the target area in cognitive studies. Currently, in many studies the protocols developed for motor cortex stimulation are transferred to stimulation of other areas, and it is implicitly assumed that the effects are equivalent. Given the above-mentioned non-linear effects of tDCS dependent on stimulation intensity, and duration, and inter-areal heterogeneity of transmitter and receptor availability, in light of a relevant impact of the latter on tDCS effects (Nitsche et al., 2012b), this assumption is not completely justified. Moreover, since the relationship between stimulation polarity and performance alteration is not homogeneous, but might depend on task characteristics, physiological data are needed to understand these interactions. This is not only important for basic science, but will also lead to improved stimulation protocols in future clinical applications. To give an example, if the prolonged anodal tDCS performed in some studies for treatment of Alzheimer´s disease (Boggio et al., 2009, 2012) indeed caused an excitability reduction, as it does in the motor cortex of healthy humans (Monte–Silva et al., 2013), this would have important implications for future stimulation protocols. Thus systematic studies are needed to define the optimal stimulation duration and intensity to modulate physiology in the intended direction, and to improve functions and disease symptoms.

Repetitive stimulation with increased total stimulation duration showed increased efficacy as compared to single sessions, which might be caused by cumulative physiological effects (Alonzo et al., 2012; Boggio et al., 2007b; Reis et al., 2009). The impact of the specific interval between tDCS sessions on physiological alterations has however so far not been extensively explored. In accordance with the induction of late phase plasticity in animal models, it might be suggested that repetition within a specific time window of approximately up to 30 min is able to stabilize after-effects of tDCS, while longer intervals might be less effective (Monte–Silva et al., 2013; Monte–Silva et al., 2010). These data were however obtained for physiological effects in the motor cortex of healthy humans, and the transferability to psychological processes and clinical symptoms remains to be explored systematically. Some pilot studies in stroke patients with anomia, and patients suffering from alcohol dependency (Klauss et al., 2014) show however encouraging preliminary results.

4.2. Electrode montage for tDCS: Focusing and beyond

The spatial resolution of conventional tDCS is considered to be relatively diffuse owing to skull dispersion. Datta et al. (2009) suggested, based on a simulation study, that electric fields may be clustered at distinct gyri/sulci sites due to details in tissue architecture/conductivity, notably cerebrospinal fluid. They analyzed the spatial focality of the conventional rectangular-electrode (7×5 cm^2), and concluded that this electrode configuration results in diffuse (unfocal) stimulation, with discrete clusters of electric field magnitude maxima. Moreover, in the respective model the peak-induced electric field magnitude was not observed directly underneath the electrodes, but at an intermediate lobe.

Nitsche et al. (2008) describe some strategies suited to increase the focality of tDCS: (i) reduction of the size of the target electrode with constant current density at the skin electrode interface; (ii) enhancement of the size of the "return" electrode, thereby decreasing current density, and reducing physiological effects; and (iii) usage of an extracephalic reference electrode montage. All of these approaches have been physiologically tested, and shown to be effective. Results of recent studies exploring vasomotor reactivity in relation to tDCS show however that the extracephalic montage seems to reduce this parameter, while a bi-cephalic montage did not result in this effect (List et al., in press; Vernieri et al., 2010). This might mean that especially in patient populations at risk, such as in stroke patients, extra-cephalic montages should be used with caution.

In the last years, some other electrode designs have been proposed to enhance focality of stimulation. High definition (HD) tDCS uses an electrode arrangement, in which the target electrode is located in the center and surrounded by four reference electrodes (Bikson et al., 2012; Caparelli–Daquer et al., 2012; Edwards et al., 2013; Kuo et al., 2013). This protocol modulates cortical excitability (Kuo et al., 2013), however, enhanced focality of the stimulation is derived from simulation data at present. Another tDCS approach suggested to reduce the "unfocal"

characteristic of this non-invasive brain stimulation is image-guided tDCS (IG-tDCS). IG-tDCS adopts a single reference electrode and an active electrode array consisting of 16 (4 × 4) sub-electrodes (Jung et al., 2013). For a selected target brain area, the optimal injection current of each arrayed sub-electrode is evaluated automatically using a *generic* algorithm in order to deliver the maximum available current to this area. Most recently, Ruffini and coworkers (Ruffini et al., 2014) suggested multifocal tDCS using modeling of electric fields for stroke and depression. They used 8 small stimulating electrodes and defined localized and spatially extended targets using resting-state functional connectivity MRI and PET data. Future studies have to show if and how these conceptual approaches are suited to induce the suggested physiological effects on cerebral neurons.

Beyond enhancing focality of tDCS, especially for modulation of cognition and behavior it should be taken into account that functional networks, and not isolated areas, contribute to these processes. Thus a qualitatively different approach might be task-adapted multi-electrode stimulation to reflect the contribution of respective networks, which has however so far not been explored systematically with tDCS.

4.3. Combination of tDCS with cognitive/behavioral interventions

For identification of tDCS protocols optimally suited to influence cognition and behavior, electrode placement, design, stimulation intensity, duration, and timing can be assumed to be relevant parameters.

With regard to electrode placement, the usual rationale is to position the target electrode over the area of interest, based on the assumption that the largest physiological effect is achieved under the electrode. Indeed, electrode position might be critical for achieving the intended effects (Nitsche et al., 2003a), however the assumption that the largest effects of tDCS are achieved under the stimulation electrodes has been challenged by recent modeling work (Datta et al., 2009), which is not in complete accordance with physiological or behavioral data in each case (Nitsche et al., 2007, 2003c).

With regard to stimulation duration, and intensity, at first sight it might be assumed that higher intensity and stronger stimulation is more efficient. Some, but not all studies support this view (Iyer et al., 2005; Kuo et al., 2008). The reason for these partially conflicting results might be that plasticity is a non-linear phenomenon, i.e. too strong induction might change its direction (Lisman, 2001). Therefore, synergistic effects of task performance and stimulation on plasticity might result in undesired effects in some instances. Here clearly systematic studies are needed, in which stimulation parameters are titrated to explore respective mechanisms.

Another important aspect which determines the impact of tDCS on cognition and behavior is the timing of stimulation relative to performance. In the majority of studies so far tDCS was performed during task performance, and had clear effects on executive tasks (Iyer et al., 2005), working memory tasks (Fregni et al., 2005; Ohn et al., 2008; Zaehle et al., 2011) and measures of learning and memory formation (Flöel, 2014; Javadi and Walsh, 2012; Nitsche et al., 2003c). However, also some studies in which tDCS was performed before task performance impacted on performance parameters (Antal et al., 2008; Ditye et al., 2012), and even stimulation after task performance was able to improve performance, when applied in a motor learning task over an area involved in consolidation (Nitsche et al., 2010). Comparative studies systematically exploring best-suited timing of stimulation are rare, however at least for learning and memory formation synergistic task- and stimulation-induced plasticity might be relevant. Here stimulation might boost task-related plasticity (Martin et al., 2014; Nitsche et al., 2003c). For tasks which do not require plasticity, but just acute task-related activity, and excitability alterations, such as attention, and working memory, timing might be less critical. However, this needs to be systematically explored. This might be relevant not only for basic research purposes, but also with regard to clinical application of tDCS.

4.4. Reducing variability of tDCS effects

The physiological, as well as functional effects of tDCS show substantial interindividual variability (Nitsche and Paulus, 2001; Wiethoff et al., 2014). With regard to basic studies, this might not be a major problem, and will primarily determine the number of subjects required for achieving significant results. However, for therapeutic application homogeneous effects are aimed for. Apart from being a problem, variability is however also an interesting phenomenon which might help us to understand the physiological basis of cognitive processes.

Some of the sources of variability of the effects of non-invasive brain stimulation have been identified during the last years. Relevant factors are handedness, sex, pharmacological effects, genetics, age, regular practice of exercise, endogenous brain oscillations, and daytime of application (Ridding and Ziemann, 2010).

For handedness, tDCS has been shown to be more effective to improve motor function of the non-dominant hand in healthy humans (Vines et al., 2008, 2006). Schade et al. (2012) showed that the modulating effects of tDCS on corticospinal excitability differ moderately according to handedness. In this study, right-handedness was associated with better effects of tDCS. With regard to sex, some minor effects on the efficacy of tDCS seem to be present, which however might differ between cortices (Chaieb et al., 2008; Kuo et al., 2006).

With regard to the impact of CNS-acting drugs on the effects of tDCS, numerous studies do exist (for an overview see Nitsche et al., 2012b), which show a clear impact of various substances, including ion channel blockers, cholinergic, dopaminergic, and serotonergic agents, amongst others. These effects are of utmost importance for clinical trials, but might be also of at least indirect importance for studies in healthy subjects, e.g. with regard to the impact of nicotine on plasticity (Grundey et al., 2012), and also with regard to slight interindividual differences with regard to receptor activities, which might be present in case of genetic polymorphisms.

With regard to genetic polymorphisms, Antal et al. demonstrated that the Val66Met BDNF polymorphism indeed has an effect on tDCS effects (Antal et al., 2010). According to a recently published study, noninvasive brain stimulation-induced cortical plasticity was affected selectively by an interaction of BDNF and COMT polymorphisms, but not by the BDNF polymorphism alone (Witte et al., 2012).

For the impact of age on tDCS effects, it was shown that stimulation intensity in children might have to be reduced to induce intended effects, since 1 mA cathodal tDCS, which reduces excitability in the adult motor cortex, enhanced it in children, but 0.5 mA tDCS resulted in the expected excitability reduction (Moliadze et al., in press). For old volunteers, tDCS seems to have similar effects on motor cortex excitability as in young volunteers (Quartarone et al., 2007). Currently available studies suggest that tDCS is functionally at least not less effective compared to young adults (Hummel et al., 2010; Zimerman et al., 2014).

Other factors, which might have an account on the impact of tDCS on cortical excitability, such as daytime of application, shape of the head, and electrode brain distance, await systematic exploration.

Taken together, a multitude of factors can have an impact on the effects of tDCS on cortical excitability. Some of them, but not

all, can be controlled for. Developing a rationale how to adjust stimulation protocols to achieve the desired effects individually will be an important future approach. Here, modeling, as well as identification of new biomarkers for the efficacy of tDCS might help.

5. Conclusions

tDCS has been recently introduced to the field of neuropsychological research, and therapeutic application. As shown in the previous sections, tDCS can be, and has been successfully applied to improve our knowledge about the physiological foundation of cognitive, affective and behavioral processes in healthy humans. Based on this knowledge, tDCS is a potentially attractive tool to alter respective clinical symptoms in patients suffering from neurological and psychiatric diseases.

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