Brain Stimulation (2008) 1, 206–23

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Transcranial direct current stimulation: State of the art 2008

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Summary
Effects of weak electrical currents on brain and neuronal function were first described decades ago. Recently, DC polarization of the brain was reintroduced as a noninvasive technique to alter cortical activity in humans. Beyond this, transcranial direct current stimulation (tDCS) of different cortical areas has been shown, in various studies, to result in modifications of perceptual, cognitive, and behavioral functions. Moreover, preliminary data suggest that it can induce beneficial effects in brain disorders. Brain stimulation with weak direct currents is a promising tool in human neuroscience and neurobehavioral research. To facilitate and standardize future tDCS studies, we offer this overview of the state of the art for tDCS.

Keywords tDCS; brain; human; neuroplasticity

Application of electrical currents to modify brain function is a very old technique, mentioned more than 200 years ago.[1,2] Systematic animal studies in anesthetized rats demonstrated that weak direct currents, delivered by intracerebral or epidural electrodes, induce cortical activity and excitability diminutions or enhancements, which can be

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Submitted April 29, 2008; revised June 2, 2008. Accepted for publication June 6, 2008.

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doi:10.1016/j.brs.2008.06.004

stable long after the end of stimulation.[3] Subsequent studies revealed that the long-lasting effects are protein synthesis-dependent[4] and accompanied by modifications of intracellular cAMP and calcium levels.[5,6] Thus, these effects share some features with the well-characterized phenomena of long-term potentiation (LTP) and long-term depression (LTD). *Transcranial* application of weak direct currents also induces intracerebral current flow sufficiently large enough to be effective in altering neuronal activity and behavior. In monkeys, approximately 50% of the transcranially applied current enters the brain through the skull.[7] These estimates were confirmed in humans.[8] Initial studies in humans aimed at treating or modifying psychiatric diseases, particularly depression. Anodal stimulation was suggested to diminish depressive symptoms,[9] while cathodal stimulation reduced manic symptoms.[10] Unfortunately, these results were not replicated in follow-up studies performed in the United Kingdom, possibly because of different patient subgroups, inconsistent stimulation parameters, or other factors that were not controlled for systematically (for an overview[1,11,12]).

In the last few decades, tDCS was re-evaluated and shown to reliably modulate human cerebral cortical function inducing focal, prolonged—but yet reversible—shifts of cortical excitability.[1,13-16] Studies combining tDCS with other brain imaging and neurophysiologic mapping methods (for example, functional magnetic resonance tomography [fMRI]; positron emission tomography [PET], or electroencephalography [EEG]) promise to provide invaluable insights on the correlation between modification of behavior and its underlying neurophysiologic underpinnings.

This review will discuss how to modify cortical excitability by tDCS with special emphasis on methodologic aspects.

Physical parameters and practical application of tDCS

tDCS differs qualitatively from other brain stimulation techniques such as transcranial electrical stimulation (TES) and transcranial magnetic stimuation (TMS) by not inducing neuronal action potentials because static fields in this range do not yield the rapid depolarization required to produce action potentials in neural membranes. Hence, tDCS might be considered a neuromodulatory intervention. The exposed tissue is polarized and tDCS modifies spontaneous neuronal excitability and activity by a tonic de- or hyperpolarization of resting membrane potential.[17,18] The efficacy of tDCS to induce acute modifications of membrane polarity depends on current density, which determines the induced electrical field strength,[18] and is the quotient of current strength and electrode size. Also, for humans it was shown that larger current densities result in stronger effects of tDCS.[13,19] Another important parameter of tDCS is stimulation duration. With constant current density, increasing stimulation duration determined the occurrence and duration of after-effects in humans and animals.[3,13-15]

Therefore tDCS protocols should state current strength and shape, electrode size, and stimulation duration for comparability between studies.

Another important parameter to achieve the intended electrical stimulation effects—probably by determining the neuronal population stimulated—is orientation of the electric field, which is defined generally by the electrodes' positions and polarity. Hereby, the anode is defined as the positively charged electrode, whereas the cathode is the negatively charged one. Current flows from the cathode to the anode. For modulation of activity or excitability in the human motor cortex, two of six different electrode position-combinations tested so far were effective. The effective combinations may have modulated different neuronal populations[13,16](for an overview of electrode montages used so far also in other cortical areas, this is discussed later in the text; Table 1). In two other studies, in which the primary visual cortex was stimulated, the placement of the second electrode over the vertex or the neck resulted in qualitatively different effects on visual-evoked potentials.[20,21] Similarly, early animal experiments showed that surface-anodal tDCS enhanced and surface-cathodal tDCS reduced activity of superficial cortical neurons, whereas neurons situated deep in the cortical sulci, and thus differently oriented, were oppositely affected.[17]

tDCS protocols should specify electrode position as accurately as possible, because different current flow directions may result in different effects. Moreover, current direction and electrode position could affect the amount of shunting and thereby alter the amount of current delivered to brain tissue. Because the induced currents in the brain will depend on and possibly be distorted by tissue characteristics,[22,23] *ultimately, realistic (for example, finite element) head models are desirable and may have to be specially constructed for the brain with large anatomic lesions.*

Direct currents have generally been delivered via a pair of sponge electrodes moistened with tapwater or NaCl solution (size between 25 and 35 cm^2 in different studies[13,16,19,24]). The use of nonmetallic electrodes (such as rubber electrodes) avoids electrochemical polarization. A recently conducted study suggests that a medium NaCl concentration (between 15 and 140 mM) is optimally suited to minimize discomfort.[25] Alternatively, electrode cream can be used to mount the electrodes on the head. Skin preparation might be helpful to reduce resistance and improve the homogeneity of the electric field under the electrodes. tDCS should be performed with a stimulator delivering constant current. Current density delivered has varied between 0.029 and 0.08 mA/cm^2 in most published studies (Table 1). These limits will probably continue to expand with experience. At the beginning of stimulation, most subjects will perceive a slight itching sensation, which then fades in most cases. Instantaneously making or breaking of the stimulating circuit results in AC current transients

Table 1 Synopsis of tDCS studies performed in humans since 1998

Stimulation protocol							
Studies	Polarity	Stimulation electrode position	Reference electrode position	Duration	Current density (mA/cm^2)	Effects	Side effects
Basic neurophysiology							
Motor cortex							
Antal et al[39]	A/C/S	M1	Contralateral orbit	10 min	0.029	Motor and cognitive tasks during the stimulation modify the effect of stimulation	None reported
Ardolino et al[40]	C/S	M1, hand area	Contralateral orbit	10 min	0.042	Excitability diminution by cathodal tDCS	None
Baudewig et al[53]	A/C	M1, hand area	Contralateral orbit	5 min	0.029	Decrease of activation of ipsilateral sma after cathodal tDCS in a finger-tapping task (fMRI)	None reported
Boros et al[29]	A/C	premotor cortex	Contralateral orbit	13 min (A), 9 min (C)	0.029	M1: Decrease of intracortical inhibition, increase of intracortical facilitation after anodal tDCS	Itching under the electrodes
Cogiamanian et al[54]	A/C/S	M1	Right deltoid muscle	10 min	0.043	Anodal tDCS increase endurance time for a submaximal isometric contraction of contralateral elbow flexors	None
Furubayashi et al[55]		M1 hand area	Contralateral orbit	100 ms, 10 min	up to 0.33	Excitability enhancement by anodal and excitability reducton by cathodal tDCS	None
Gandiga et al[26]	A/C/S	M1 hand area	Contralateral orbit	20 min	0.04	Effects on attention, fatigue and discomfort to evaluate the sham procedure. There was no difference between sham and real stimulation	One subject headache, slight tingling sensation under the electrode
Jeffery et al[56]	A/C	M1, leg area	Contralateral orbit	10 min	0.06	Excitability enhancement for more than 60 min after anodal tDCS	Sensation under the electrodes
Kuo et al[57]	A/C	M1, hand area	Contralateral orbit	13 min (A), 9 min (C)	0.029	Rivastigmine abolishes anodal and stabilises cathodal after-effects on excitability	None reported
Kuo et al[58]	A/C	M1, hand area	Contralateral orbit	13 min (A), 9 min (C)	0.029	l-dopa turns anodal tDCS-induced excitability enhancement into inhibition and stabilises cathodal after-effects on excitability	None reported
Kuo et al[35]	A/C	M1, hand area	Contralateral orbit	4 s A/C, 13 min (A), 9 min (C)	0.029	Females show more inhibition during and after cathodal tDCS as compared to males	None reported
Kwon et al[59]	A/non	M1, hand area	Contralateral orbit	21 s	0.141	BOLD-activation in left hand area of M1, left sma and right parietal cortex	Slight tingling sensation under the electrode
Lang et al[60]	A/C/S	M1, hand area	Contralateral orbit	10 min	0.029	PET shows widespread decreases and increases of rCBF in multiple cortical and subcortical areas	None reported, subjects unable to distinguish real from sham tDCS

Lang et al[61]	A/C	M1, hand area	Contralateral orbit	10 min	0.029	Polarity-dependend effetcs of tDCS on left M1 and transcallosal inhibition, no effetcs on right M1	None reported
Lang et al[62]	A/C/S	M1, hand area	Contralateral orbit	10 min	0.029	Preconditioning tDCS modifies 5 Hz- rTMS after-effects (homeostatic plasticity)	None reported
Liebetanz et al[63]	A/C	M1, hand area	Contralateral orbit	5 min	0.029	Riluzole (one dosage) does not influence tDCS	None reported
Liebetanz et al[64]	A/C	M1, hand area	Contralateral orbit	5 min	0.029	Carbamazepine suppresses the excitability enhancement after anodal tDCS, dextromethorphane also the after-effects of cathodal tDCS	Itching under the electrodes
Nitsche et al[65]	A/C	M1, hand area	Contralateral orbit	7 min A/C, 15 min (A)	0.029	Anodal tDCS enhances, cathodal tDCS reduces the excitability-enhancing effect of PAS25, if applied before PAS, reversed effect if both protocols are applied simultaneously	None reported
Nitsche et al[27]	A/C	M1, hand area, contralateral orbit	Contralateral orbit, Cz	4 s, 7 min A/C; 10 min A/C	0.029 (stimulation electrode), 0.01 (reference electrode)	Reducing electrode size makes motor cortical effects of tDCS more focal; reduction of current density under reference electrode makes this electrode functionally inert	None reported
Nitsche et al[66]	A/C	M1, hand area	Contralateral orbit	13 min (A), 9 min (C)	0.029	D2 receptor blocking by sulpiride abolished the induction of after-effects nearly completely. Enhancement of D2 receptors by pergolide consolidated tDCS-generated excitability diminution	Itching under the electrodes
Nitsche et al[42]	A/C	M1, hand area	Contralateral orbit	4 s, 7 min, 9 min (C), 13 min (A)	0.029	Resting and active motor thresholds remained stable during and after tDCS. The slope of the input–output curve was increased by anodal tDCS and decreased by cathodal tDCS. Anodal tDCS of the primary motor cortex reduced intracortical inhibition and enhanced facilitation after tDCS but not during tDCS. Cathodal tDCS reduced facilitation during, and additionally increased inhibition after its administration. During tDCS, I-wave facilitation was not influenced but, for the after-effects, anodal tDCS increased I-wave facilitation	Itching under the electrodes, light flashes, when current was turned on or off
Nitsche et al[67]	A/C	M1, hand area	Contralateral orbit	13 min (A), 9 min (C)	0.029	d-cycloserine selectively potentiated the duration of motor cortical excitability enhancements induced by anodal tDCS.	Itching under the electrodes

(*continued*)

Table 1 (*continued*)

Stimulation protocol							
Studies	Polarity	Stimulation electrode position	Reference electrode position	Duration	Current density (mA/cm^2)	Effects	Side effects
Nitsche et al[49]	A/C	M1, hand area	Contralateral orbit	13 min (A), 9 min (C)	0.029	MRI performed 30 and 60 min after tDCS did not show pathological signal alterations in pre- and post-contrast-enhanced T1-weighted and diffusion-weighted MR sequences	None
Nitsche et al[68]	A/C	M1, hand area	Contralateral orbit	4 s A/C; 5 min A/C;11 min (A), 9 min (C)	0.029	Lorazepam did not influence intra-tDCS effects, resulted in a delayed, but then enhanced and prolonged anodal tDCS-induced excitability elevation for the after-effects	Itching under the electrodes, light flashes, when current was turned on or off
Nitsche et al[69]	A/C	M1, hand area	Contralateral orbit	4 s A/C; 5 min A/C;11 min (A), 9 min (C)	0.029	Amphetamine significantly enhanced and prolonged increases in anodal, tDCS-induced, long-lasting excitability enhancement	Itching under the electrodes
Nitsche et al[70]	A/C	M1, hand area	Contralateral orbit	4 s A/C;11 min (A), 9 min (C)	0.029	Carbamazepine selectively eliminated the excitability enhancement induced by anodal stimulation during and after tDCS. Flunarizine resulted in similar changes. Antagonising NMDA receptors did not alter current-generated excitability changes during a short stimulation, which elicits no after-effects, but prevented the induction of long-lasting after-effects independent of their direction.	Itching under the electrodes, light flashes, when current was turned on or off
Nitsche and Paulus[13]	A/C	M1, hand area	Contralateral orbit	4s, 1-5 min	0.006-0.029	Excitability enhancement by anodal, diminution by cathodal tDCS, duration dependent on tDCS duation	None reported
Nitsche and Paulus[14]	A	M1, hand area	Contralateral orbit	5-13 min	0.029	Excitability enhancement dependent on stimulation duration, 13 min anodal tDCS elicits 90 min after-effects, sNSE not enhanced	None reported
Nitsche et al[15]	C	M1, hand area	Contralateral orbit	5-9 min	0.029	Excitability diminution dependent on stimulation duration, 9 min cathodal tDCS elicits 60 min after-effects, sNSE not enhanced	Itching under the electrodes
Power et al[71]	A/C/S	M1, hand area	Contralateral orbit	10 min	0.029	Intermuscular coherence: ß-band enhanced after anodal, reduced after cathodal tDCS	None reported

Priori et al[16]	A/C	M1, hand area	Chin	7 sec	0.003-0.02	Excitability diminution by anodal tDCS after cathodal tDCS	None
Priori et al[1]	C	M1, hand area	Contralateral orbit	10 min	0.029	Excitability diminution by cathodal tDCS	None reported
Quartarone et al[72]	A/C/S	M1, hand area	Contralateral orbit	5 min	0.029	Cathodal tDCS decrease MEP amplitudes with and without motor imagery, anodal tDCS enhances MEP amplitudes only without motor imagery	None reported
Siebner et al[33]	A/C/S	M1, hand area	Contralateral orbit	10 min	0.029	Preconditioning tDCS modifies 1 Hz- rTMS after-effects (homeostatic plasticity)	None reported
Somatosensory cortex							
Antal et al[73]	A/C/S	S1	Contralateral orbit	15 min	0.029	Cathodal stimulation diminished laser-evoked pain perception and the amplitude of N2 component of LEPs	None reported
Dieckhöfer et al[74]	A/C	S1	Contralateral orbit	9 min	0.042	Reduction of N20 of median nerve SEPs after cathodal tDCS up to 60 min after tDCS	Tingling under the electrodes
Matsunaga et al[41]	A/C	M1, hand area	contralateral orbit	10 min	0.029	Amplitudes of P25/N33, N33/P40 (parietal components) and P22/N30 (frontal component) following median nerve stimulation were significantly increased for 60 min after anodal tDCS, no effect of cathodal tDCS	Itching under the electrodes
Ragert et al[75]	A/S	S1	Contralateral orbit	20 min	0.04	Improved spatial acuity	None reported
Rogalewski et al[76]	A/C	C4	Contralateral orbit	7 min	0.029	Cathodal stimulation compared with sham induced a prolonged decrease of tactile discrimination, while anodal and sham stimulation did not	Itching under the electrodes
Terney et al[77]	A/C/S	M1	Contralateral orbit	10 min	0.029	Pergolide increased the efficacy of cathodal tDCS to reduce the amplitude of laser-evoked potentials	None reported
Visual cortex							
Accornero et al[20]	A/C	Oz	neck	3/10 min	0.025	N100-decrease by anodal and-increase by cathodal tDCS	None
Antal et al[78]	A/C	Oz	Cz	7 min	0.029	Elevated visual perception threshold by cathodal tDCS	None reported
Antal et al[79]	A/C	Oz	Cz	10 min	0.029	Phosphene threshold reduced by anodal and increased by cathodal tDCS	None reported
Antal et al[80]	A/C	Oz	Cz	10 min	0.029	Moving phosphene threshold reduced by anodal and increased by cathodal tDCS	None reported
Antal et al[21]	A/C	Oz	Cz	5-15 min	0.029	Elevated N70 amplitude by anodal and reduced N70 amplitude by cathodal tDCS	None reported

(*continued*)

Table 1 (*continued*)

Stimulation protocol							
Studies	Polarity	Stimulation electrode position	Reference electrode position	Duration	Current density (mA/cm^2)	Effects	Side effects
Antal et al[81]	A/C	Oz	Oz vs Cz	10 min	0.029	Elevated gamma and beta oscillatory activities by anodal and reduced by cathodal tDCS	None reported
Antal et al[82]	A/C/S	Oz, left V5	Cz	10 min	0.029	Both cathodal and anodal stimulation over MT +/V5 resulted in a significant reduction of the perceived MAE duration, but had no effect on performance in a luminance-change-detection task	None reported
Lang et al[83]	A/C/S	Oz	Cz	10 min	0.029	The priming effect of tDCS on rTMS over the visual cortex is modest compared to the motor cortex	None reported
Cognitive/behavioural							
Learning/memory							
Antal et al[84]	A/C	Left V5, M1	Cz, Contralateral orbit	7 min	0.029	Improved visuo-motor performance by cathodal tDCS, modified motion perception threshold by anodal and cathodal tDCS	None reported
Antal et al[85]	A/C	Left V5, M1	Cz, Contralateral orbit	10 min	0.029	Improved visuo-motor learning by anodal tDCS	None reported
Boggio et al[86]	A/S	M1, hand area	Contralateral orbit	20 min	0.029	Anodal tDCS on non-dominant M1 improved motor function.	None reported
Boggio et al[87]	A/S	M1, left DLPFC	Contralateral orbit	20 min	0.029 or 0.057	Improvement in working memory of Parkinsońs disease patients after anodal tDCS of the LDLPFC with 2 mA but not with 1 mA.	None reported
Boggio et al[88]	A/S	DLPFC, Occiptal cortex	Supraorbital area	20 min	0.057	Left DLPFC anodal stimulation of depressive patients induced an improvement in an affective go-no-go task.	Mild adverse events equally distributed across the 3 groups (headache, itching, redness of skin).
Fecteau et al[89]	A/C/S	left or right DLPFC	Left, right DLPFC, or Contralateral orbit	20 min	0.057	Bilateral DLPFC tDCS with an anodal electrode over the right or the left DLPFC (with cathodal electrode over the homologous area of the contralateral hemisphere) resulted in a risk-averse response style compared to those with sham or unilateral DLPFC stimulation.	Slight itching sensation.
Fecteau et al[90]	A/C/S	left or right DLPFC	right or left DLPFC	15 min	0.057	Right anodal/left cathodal tDCS resulted in safer responses.	Slight itching sensation

Ferrucci et al[32]	A/C/S	Cerebellum (2 cm under the inion, 1 cm posterior to the mastoid process)	Right deltoid muscle	15 min	0.095	Anodal and cathodal tDCS impairs the practice-dependent proficiency in working memory	1 subject headache (cathodal tDCS)
Flöel et al[91]	A/C/S	Cp5	Contralateral orbit	20 min	0.029	Enhanced language learning by anodal tDCS	None reported
Fregni et al[43]	A/C/S	M1, DLPFC	Contralateral orbit	10 min	0.029	Left DLPFC anodal tDCS leads to an enhancement of working memory performance.	None reported
Fregni et al[92]	A/S	Left DLPFC	Contralateral orbit	20 min (5days)	0.029	Working memory improvement after anodal tDCS on depressive patients.	None reported
Iyer et al[19]	A/C/ sham	F3	Contralateral orbit	20 min	up to 0.08	Enhanced verbal fluency by anodal tDCS	Skin redness
Kincses et al[93]	A/C/no	Fp3	Cz	10 min	0.029	Anodal tDCS enhanced probabilistic classification learning	None reported
Kuo et al[94]	A/C	M1, hand area	Contralateral orbit	10 min	0.029	No Impact of tDCS on SRTT and in a simple reaction time task, if tDCS applied before task performance	None reported
Lang et al[95]	A/C	M1, hand area	Contralateral orbit	app. 10 min	0.029	Anodal tDCS affects recall performance after motor sequnece learning	None reported
Marshall et al[96]	A/non	F3 and F4	Both mastoids	15 sec off/15 sec on over 30 min	0.52	Anodal tDCS during slow wave sleep improves declarative verbal memory	None
Marshall et al[97]	A/C/ non	F3 and F4	Both mastoids	15 sec off/15 sec on over 15 min	0.52	Impaired performance in Sternberg-task by anodal and cathodal tDCS	None reported
Nitsche et al[98]	A/C	M1, hand area premotor, prefrontal, frontoplolar cortex	Contralateral orbit	About 10 min	0.029	Anodal stimulation of the primary motor cortex during SRTT ans RTT performance resulted in increased performance, whereas stimulation of the remaining cortices had no effect.	Itching under the electrodes
Ohn et al[99]	A/S	F3	Contralateral orbit	30 min	0.04	Anodal tDCS enhanced performance in a 3 letter back working memory task	None
Rosenkranz et al[100]	A/C	M1, hand area	Contralateral orbit	5 min	0.029	With tDCS of anodal and cathodal polarity motor training-induced directional change of thumb movements was reduced during a 10 min post-training interval	None reported
Sparing et al[101]	A/C/S	Cp5	Cz	7 min	0.06	Improved picture naming by anodal tDCS	None
Social cognition							
Knoch et al[31]	C	right DLPFC (F4)	Contralateral orbit	About 14 min (4 min before and during task performance	0.043 (stimulation electrode) 0.015 (reference)	Less propensity to punish unfair behavior	None reported

(*continued*)

Table 1 (*continued*)

Stimulation protocol							
Studies	Polarity	Stimulation electrode position	Reference electrode position	Duration	Current density (mA/cm^2)	Effects	Side effects
Priori et al[102]	A/C/S	Bilateral DLPFC	Right deltoid muscle	10 min	0.046	Anodal tDCS over DLPFC influences experimental deception	None
Perception							
Varga et al[103]	A/C/S	P6-P8	Cz	10 min	0.029	Cathodal stimulation reduced the duration of gender specific after-effect	None reported
Clinical							
Migraine							
Antal et al[104]	A/C	M1	Contralateral orbit	10 min	0.029	Short term homeostatic plasticity is altered in patients with migraine	None reported
Chadaide et al[105]	A/C/S	Oz	Cz	10 min	0.029	Cathodal stimulation had no effect on phosphene thresholds in migraineurs	None reported
Depression							
Fregni et al[106]	A/S	Left DLPFC	Contralateral orbit	20 min (5 days)	0.029	Anodal tDCS leads to a significant decrease in depression scores.	None reported
Boggio et al[107]	A/S	Left DLPFC, occipital cortex	Contralateral supraorbital area	20 min (10 days)	0.057	Anodal tDCS leads to a significant decrease in depression scores that lasts for at least 30 d after the end of treatment.	Mild adverse events equally distributed across the 3 groups (headache, itching, redness of skin).
Rigonatti et al[108]	A/S	Left DLPFC	Contralateral supraorbital area	20 min (10 days)	0.057	Antidepressant effects of tDCS were similar to those of a 6-week course of fluoxetine (20 mg/day)	None reported
Stroke							
Boggio et al[44]	A/C/S	M1 (hand area) of the affected (anodal) or unaffected (cathodal) hemisphere	Contralateral supraorbital area	20 min (4 weekly sessions or 5 consecutive daily sessions)	0.029	Anodal or cathodal tDCS leads to a motor improvement. Consecutive daily sessions but not weekly sessions were associated with a cumulative motor improvement that lasted for 2 weeks.	None reported
Fregni et al[109]	A/C/S	M1	Contralateral orbit	20 min	0.029	Both cathodal stimulation of the unaffected hemisphere and anodal stimulation of the affected hemisphere improved motor performance.	None reported
Hesse et al[110]	A	C3/C4	Contralateral orbit	7 min	0.04	Improvement of arm function in patients with paresis after stroke, when tDCS was combined with arm training, improvement of aphasia	Slight itching under electrode, headache
Hummel et al[24]	A/S	M1, hand area	Contralateral orbit	20 min	0.04	Anodal tDCS improved the performance of a test mimicking activities of daily living with the paretic hand of chronic stroke patients	Slight tingling sensation under the electrode

Hummel et al[111]	A/S	M1, hand area	Contralateral orbit	20 min	0.04	Anodal tDCS improved the performance of simple motor functions such as pinch force and reaction times in chronic stroke patients. The improvement was more pronounced in the more impaired patients.	Slight tingling sensation under the electrode
Monti et al[112]	A/C/S	Left fronto-temporal area	Right deltoid muscle	10 min	0.057	Improvement of naming in patients with chronic non-fluent aphasia by cathodal tDCS	None reported
Parkinson's disease							
Fregni et al[113]	A/C/S	M1, hand area DLPFC	Contralateral orbit	20 min	0.029	Anodal tDCS of M1 but not cathodal or DLPFC tDCS improved motor function. Anodal stimulation of M1 increased MEP amplitude and area and cathodal stimulation of M1 decreased them.	None reported
Pain							
Fregni et al[45]	A/S	M1	Contralateral orbit	20 min (5 days)	0.057	Pain improvement after anodal stimulation over M1 of patients with central pain due to traumatic spinal cord injury.	None reported
Fregni et al[114]	A/S	M1, DLPFC	Contralateral orbit	20 min (5 days)	0.057	Anodal tDCS of M1 induced greater pain improvement compared with sham stimulation and stimulation of the DLPFC of patients with fibromyalgia. This effect was still significant after 3 weeks of follow up.	The frequency of adverse effects (sleepness, itching,and headache) was not different across the three conditions of treatment.
Roizenblatt et al[115]	A/S	Left M1 or DLPFC	Contralateral supraorbital area	20 min (5 days)	0.057	M1 tDCS increased sleep efficiency and decreased arousals. DLPFC tDCS was associated with a decreased sleep efficiency, an increase in rapid eye movement and sleep latency. The decrease in REM latency and sleep efficiency were associated with an improvement in fibromyalgia symptoms.	None reported
Craving							
Boggio et al[116]	A/C/S	Left or right DLPFC	Left or Right DLPFC	20 min	0.057	Both anodal left/cathodal right and anodal right/cathodal left decreased alcohol craving compared to sham stimulation. Following treatment, craving could not be further increased by alcohol cues.	The frequency of adverse effects (discomfort, headache, mood changes, and itching) was not different across the three conditions of treatment.
Fregni et al[117]	A/C/S	Left or right DLPFC	Left or Right DLPFC	20 min	0.057	Craving for viewed foods was reduced by anode right/cathode left tDCS. Compared with sham stimulation, subjects fixated food-related pictures less frequently after anode right/cathode left tDCS and consumed less food after both active stimulation conditions.	Few mild adverse events, but with the same frequency in the active and sham tDCS groups.

(*continued*)

Table 1 (*continued*)

Stimulation protocol							
Studies	Polarity	Stimulation electrode position	Reference electrode position	Duration	Current density (mA/cm^2)	Effects	Side effects
Fregni et al[118]	A/S	Left or right DLPFC	Homologue area. Cathodal electrode of 100 cm^2	20 min	0.057	Both left and right DLPFC tDCS, but not sham, reduced smoking craving after cue-exposition.	The frequency of adverse effects (drowsiness, itching, headache, scalp burning, concentration problems, mood changes, tingling) was not different across the three conditions of treatment.
Diverse							
Ferrucci et al[119]	A/C/S	P3-T5, P4-T6	Deltoid muscle	15 min	0.06	Improved word recognition in Alzheimeŕs disease by anodal and worsened performance by cathodal tDCS	Tingling under electrodes
Fregni et al[120]	A/C/S	Left temporoparietal area	Contralateral Supraorbital area	3 min	0.029	Anodal tDCS of LTA resulted in a reduction of tinnitus.	None reported
Huey et al[121]	A/S	F3	Contralateral orbit	40 min	0.08	No effect on verbal fluency in frontotemporal degeneration	None reported
Quartarone et al[37]	A/C	M1, hand area	Contralateral orbit	10 min	0.029	Lack of tDCS after effects in ALS patients	None reported
Quartarone et al[122]	A/C/S	M1, hand area	Contralateral orbit	10 min	0.029	Lack of inhibition by cathodal tDCS in patients with focal dystony, no clear homeostatic effect with consecutive rTMS	None

Here the studies performed in healthy subjects as well as patients with neuropsychiatric diseases during the last years are gathered. Studies are grouped for basic neurophysiology, cognitive/behavioral and clinical. For each study, the stimulation protocol including electrode position, stimulation polarity, stimulation duration, current density as well as results and side effects are mentioned. Note that the term *reference electrode* does not mean that this electrode is functionally inefficient, when positioned over the brain, but refers to the fact that this electrode is not positioned over the cortical area intended to modulate in a specific experiment. A = anodal tDCS; C = cathodal tDCS; S = sham tDCS. Electrode position refers to the international 10 20 system, if appropriate. M1 = primary motor cortex; S1 = primary somatosensory cortex; DLPFC = dorsolateral prefrontal cortex.

that cause neuronal firing. This is noticeable as brief retinal phosphenes with electrodes near the eyes, but can cause other sensations with other electrode locations, including a startle-like phenomenon when the reference electrode is located off the head (E.M.W., February 28, 2008, personal communication, written). These effects can be avoided by ramping the current up and down at the beginning and end of treatment. *For tDCS, electrodes, which are not subject to electrochemical effects such as electrolysis are preferable. The contact between electrodes and scalp can be made by water-soaked sponges or electrode cream. Current ramping is recommended to prevent electrical transients.*

tDCS focality is limited by (a) using large electrodes[26] and (b) the bipolar scalp electrode arrangement used in many studies. Because of the large electrode size, tDCS might not only stimulate the intended, but also adjacent cortical areas. Moreover, a cephalic reference electrode might also effectively modulate remote areas. Note that because usually one electrode is defined as the reference and the other as the stimulation electrode. Since both electrodes have similar current and both are placed on the scalp, this is a functional definition and does not imply that the "reference" electrode is physiologically inert. The issue of an active reference is less important when the hypothesis under study is anatomically constrained; for example, when testing motor cortex excitability with TMS, but can be problematic in other studies.

To increase focality, electrode size can be reduced. Primary motor cortex excitability can be altered effectively with a 3.5 cm^2-sized electrode holding current density constant. When compared with a large 35 cm^2-sized electrode, the small electrode resulted in a much more spatially limited excitability modification.[27] However, the effects of small electrodes could differ qualitatively due to: (a) differential shunting of current in the scalp; (b) greater edge-effect relative to the overall electrode area (antagonistically oriented electric fields in the immediate vicinity of the electrodes[28]); and other factors.[23] For the motor cortex, it was shown that a smaller electrode modulates corticospinal excitability similarly to a larger one, but the effects on intracortical inhibition and facilitation were abolished and the variability of the effects was larger.[29]

One means of reducing the effect of a cephalic reference electrode is to increase its size, thus reducing current density, and consequently its efficacy. Increasing the size of this electrode threefold in relation to the "stimulation" electrode, the latter delivering a current density of 0.029 mA/cm^2, made stimulation of this site functionally inert[27] and was used in previous behavioural studies.[30,31] As mentioned previously for smaller electrodes, enlarging the electrode might also affect shunting and current orientation. Therefore, these factors should be considered when designing a study. Alternatively, an extracephalic reference can be used to avoid the confounding effects of two electrodes with opposite polarities over the brain.[20,32] Because current orientation with respect to the target cells determines the effects of tDCS, results achieved by these protocols might differ from those with cephalic references.[13,16,20,21] *Increasing focality of tDCS can be achieved by: (1) reducing electrode size, but keeping current density constant, for the electrode that is intended to affect the underlying cortex; (2) increasing the size, and thus reducing current density, of the electrode, which should not affect the underlying cortex; or (3) using an extracephalic reference. Each of these approaches implies methodologic differences that might lead to qualitatively different effects of the stimulation.*

Compared with TMS, it is easier to conduct placebo stimulation-controlled studies with tDCS, because, with the exception of a slight itching sensation and sensory phenomena, including retinal phosphenes with current switching, subjects rarely experience sensations related to the treatment.[26] To reduce cutaneous sensation and other transient phenomena at the start and stop of stimulation, current flow should be ramped up and down. This might also prevent the dizziness or vertigo occasionally reported after exposure. For sham stimulation, tDCS can be delivered for several seconds and then discontinued, because most subjects feel the itching sensation only initially during tDCS.[33] Ramping for 10 seconds at the beginning and end of tDCS, combined with a stimulation duration of 30 seconds in the placebo stimulation condition, made real tDCS (performed over 20 minutes) and placebo stimulation indistinguishable.[26] In another study that used a similar sham stimulation condition, only about 17% of subjects could distinguish between real and sham tDCS.[34] Brief tDCS performed as previously described for sham treatment does not appear to alter brain function. Because stimulators can be programmed to deliver sham tDCS protocols, double-blinded experimental designs should be standard in this field. Therefore, one member of the laboratory should program the stimulator, while another performs the stimulation. For short-lasting stimulation, when ramping is not possible, or more intense protocols, which might increase somatosensory sensations, topical application of local anesthetics might prevent any somatosensory perception and thus evolve as an alternative (A.P. and M.A.N., February 28, 2008, personal communication, oral). *To achieve better satisfactory blinding of the subjects, tDCS should be started and terminated after a few seconds in a ramp-like fashion to minimize sensations. Even then, some subjects may still be able to discern between real and sham stimulation and thus post hoc questioning of subjects may be important to assess the effectiveness of blinding, especially in cross-over experimental designs and all therapeutic trials.*

If interindividual comparisons are made, the subject groups should be matched for sex and age, because there seems to be sex differences regarding the efficacy of tDCS. For motor cortex stimulation, cathodal tDCS was more effective in women, whereas anodal tDCS was more effective in the visual cortex in women as compared with men[35,36] (A.P., March 10, 2008, personal communication,

oral). An age dependency for tDCS efficacy has not been described so far,[37] but cannot be excluded at present, viz experience with TMS.[38] Uncontrolled interference with ongoing cortical activity during tDCS should be avoided. It has been demonstrated for motor cortex tDCS that extensive cognitive effort unrelated to the stimulated area as well as massive activation of the stimulated motor cortex by prolonged muscle contraction abolishes the effects of tDCS.[39] *Subject groups should be matched or randomized according to factors, which could influence the efficacy of tDCS. The state of the subjects and their activities before, during, and after tDCS should be controlled for, to avoid uncontrolled interference of those factors with tDCS.*

Time course of tDCS-induced modulations of cortical excitability

In the primary motor cortex, the dependence of the efficacy of tDCS from current density and stimulation duration has been systematically explored. Increasing current density or stimulation duration, holding the other parameter constant, results in longer-lasting and stronger effects.[13-15] For increased current density, however, this might not be a linear relationship in each case, because larger current densities will increase the depth of the electrical field relevantly and thus alter excitability of cortical neurons not affected by lower stimulation intensities. The effect on these neurons might be different compared with superficial ones.[17] Moreover, large current densities might be painful. *Because increasing current density will increase cutaneous pain sensation and might affect different populations of neurons (because the larger the current density, the greater the depth penetration of the effective electrical field), it is suggested to increase stimulation duration and not current density, if a prolongation of the effects of tDCS for an extended time course is wanted.*

As shown for the motor cortex, anodal or cathodal tDCS performed for seconds results in a motor cortical excitability increase or decrease during tDCS, which does not outlast the stimulation itself.[13,16] With two electrodes over the scalp, tDCS with the anode positioned over the primary motor cortex and the cathode over the contralateral orbit, thus causing an anterior-posterior directed current flow, enhances, whereas the reversed electrode position with the cathode over the primary motor cortex and thus a posterior-anterior current flow reduces excitability. By using a motor cortex-chin electrode montage, anodal or cathodal tDCS alone did not shift MEP amplitudes[16]: With this montage, however, a paradoxical diminution of corticospinal excitability could be achieved when anodal stimulation was preceded by cathodal stimulation.[16] Neither the concept of immediate current flow switching nor this chin montage have been pursued any further, the authors of the first paper combining TMS as measurement tool with tDCS[16] now favor an extracranial reference electrode. *Short applications of anodal or cathodal tDCS result in excitability shifts during stimulation, but no after-effects. The direction of the excitability shift might be divergent, dependent not only on stimulation polarity, but also the specific electrode montage.*

When applied for several minutes, tDCS produces lasting effects in the human motor cortex. These are stable for up to about an hour if tDCS is applied for 9-13 minutes.[13-15,40] Anodal stimulation enhances, whereas cathodal tDCS diminishes excitability, as measured by motor-evoked potential (MEP) amplitude. Moreover, cathodal tDCS increases power in the delta- and theta bands of the EEG.[40] Outside the motor cortex, electrophysiologic studies show analogous effects of anodal tDCS on somatosensory-evoked potentials,[41] and for anodal and cathodal tDCS on visual cortex stimulation.[21] However, in the visual cortex, the excitability changes were somewhat shorter than in the motor cortex. *In summary, the duration of the excitability changes induced by tDCS depends on stimulation duration. Given a constant current density, brief exposure to tDCS for seconds did not induce after-effects, whereas about 10-minute tDCS elicits after-effects. The exact duration of effects elicited by a certain course of tDCS likely depends on the targeted cortical area; thus motor cortical effects cannot be quantitatively extrapolated to visual or other brain regions.*

If repeated sessions of tDCS are performed and cumulative effects are not the goal of a given study, the intersession interval has to be sufficiently long to avoid carry-over effects. For 4 seconds of tDCS, which elicits no after-effects, a break of 10 seconds between each period of stimulation is sufficient.[13] For tDCS durations that produce short-lasting (namely, for about 10 minutes) after-effects, a 1-hour break between stimulation sessions is sufficient.[42] For tDCS durations resulting in long-lasting after-effects (1 hour or more), an intersession interval of 48 hours to 1 week has been suggested.[14,15,43] If repetitive tDCS is performed to prolong and stabilize long-lasting after-effects, subjects are generally stimulated once a day. Indeed, it was demonstrated that behavioral effects of tDCS could be increased and made stable by this procedure.[44,45] However, whether this protocol is optimally suited to maximize the electrophysiologic effects of tDCS is not known. *For repeated application of tDCS, we suggest a sufficiently long intersession interval between tDCS courses to avoid unintended carry-over effects. The duration of this interval depends on the stimulation procedure. If the aim is to induce more stable changes in cortical function, repeated daily tDCS sessions may be adequate. However, further studies to explore the optimal intersession interval for stabilizing effects are needed.*

Safety of tDCS

Although tDCS differs in many aspects from pulsed electrical stimulation, for example, a much lower current density is applied, the stimulation does not produce time-

locked neuronal firing, and thus comparability between the different methods of stimulation is limited. Studies with pulsed electrical stimulation have identified some possible sources of tissue damage, whose relevance for tDCS will now be discussed.

Generation of electrochemically produced toxins and electrode dissolution products at the electrode-tissue interface[46] are only risks of tDCS for the skin contact, because there is no brain-electrode interface. If tDCS is performed with water-soaked sponge electrodes, chemical reactions at the electrode-skin-interface should be minimized. However, it was reported recently that repeated daily tDCS with a current density of about 0.06 mA/cm^2 caused clinically significant skin irritation under the electrodes in some patients (A.P., F.P., W.P., F.F., March 10, 2008, personal communication, oral). Thus, subjects should be specifically interviewed for the existence of skin diseases (also in the past) and the condition of the skin under the electrodes should be inspected before and after tDCS. The usually seen mild redness under the electrodes is not a hint of skin damage, but most probably caused by neurally driven vasodilation.[47] Theoretically, deposition of charge and electrolysis, generation of toxic ionic species, or modification of proteins and amino acids in brain tissue could also cause tissue damage, but these effects are thought to be unlikely caused by the high perfusion level of the brain and the buffering capacity of tissue. Moreover, there is no evidence for tDCS having such an effect. However, if stimulation is applied above the skull defect, foramina, or open fontanels or fissures in infants, or if the electrode contact is inadequate, current flow might be focused, the effective electrode size diminished, and, if current density were large enough, it could cause tissue damage.[7]

Conventional electrical brain stimulation can cause excitotoxic damage to overdriven neurons.[46] This is not applicable to tDCS for the following reasons: (1) The effects of tDCS inducing changes in cortical excitability are most probably caused by a mild effect on cation channels and not being able to induce firing in cells that are not spontaneously active; and (2) tDCS has been shown in animals to increase spontaneous neuronal firing rate only to a moderate degree, for example, within the physiologic range[3] and is unlikely to reach the threshold for excitotoxicity, even over long periods. In any case, such an excitotoxic effect would be DC polarity dependent. Because there have been few adverse events with tDCS, there have been no studies aimed at defining the limits of safety. However, some safety studies have been undertaken for frequently used tDCS protocols (current density up to 0.029 mA/cm^2, stimulation duration up to 13 minutes). These parameters do not (1) cause heating effects under the electrode[13]; (2) elevate serum neurone-specific enolase level,[14,15] a sensitive marker of neuronal damage[48]; and (3) result in changes of diffusion weighted or contrast-enhanced magnetic resonance imaging (MRI), EEG activity, or cognitive distortion.[19,49] Moreover, these protocols were tested in more than 2000-3000 subjects in laboratories worldwide with no serious side effects, except for a slight itching under the electrode, and seldom-occurring headache, fatigue, and nausea.[34] It is also possible that longer-lasting protocols are safe, because stimulation of up to 50 minutes did not cause either cognitive or emotional disturbances in healthy subjects (E.M.W., February 28, 2008, personal communication, written).

Some additional precautions should be considered for safe stimulation: electrode montages that could result in brainstem or heart nerve stimulation might be dangerous under certain conditions. While delivering current to healthy subjects via bifrontal electrodes with the reference on the leg, Lippold and Redfearn[50] encountered one case of respiratory and motor paralysis with cramping of the hands, accompanied by nausea. There was no loss of consciousness, and respiration returned when the current was stopped. The subject was not hospitalized, but had impaired fine motor control lasting for two days, ultimately returning to normal. There were no other serious adverse events in the study and apparently this subject received 10 times the intended amperage, probably 3 mA (L.B., March 28, 2008, personal communication to E.M.W., written). This scenario does not apply for currently used protocols. The stimulation device should guarantee a constant current strength, because current strength determines the intensity of the electrical field in tissue and a constant voltage device could result in unwanted increases in current strength, if resistance decreases. Stimulation durations, which are likely to result in excitability changes lasting more than 1 hour, should be applied with caution, because changes lasting that long could be consolidated and stabilized, leading to unintended or adverse effects. The same applies for repeated application of tDCS to the same brain region without an appropriate interval between sessions. Painful stimulation, which might occur with significantly higher current densities than those in current use, should be avoided. Because experience with tDCS is still limited, and the risk profile of stimulation is not completely known so far, personnel conducting tDCS should be appropriately trained before applying the technique. tDCS in patients should be supervised by a licensed medical doctor. *Extensive animal and human evidence and theoretical knowledge indicate that the currently used tDCS protocols are safe. However, knowledge about the safe limits of duration and intensity of tDCS is still limited. Thus, if charge or current density is exceeded greatly beyond the currently tested protocols, which might be desirable, for example, for clinical purposes, we suggest concurrent safety measures.*

For tDCS studies with healthy subjects, general exclusion criteria available for electrical stimulation apply: Subjects should be free of unstable medical conditions, or any illness that may increase the risk of stimulation, for example, neurologic diseases such as epilepsy or acute exzema under the electrodes. Furthermore, they should have no metallic implants near the electrodes. Subjects have to be informed about the possible side effects of

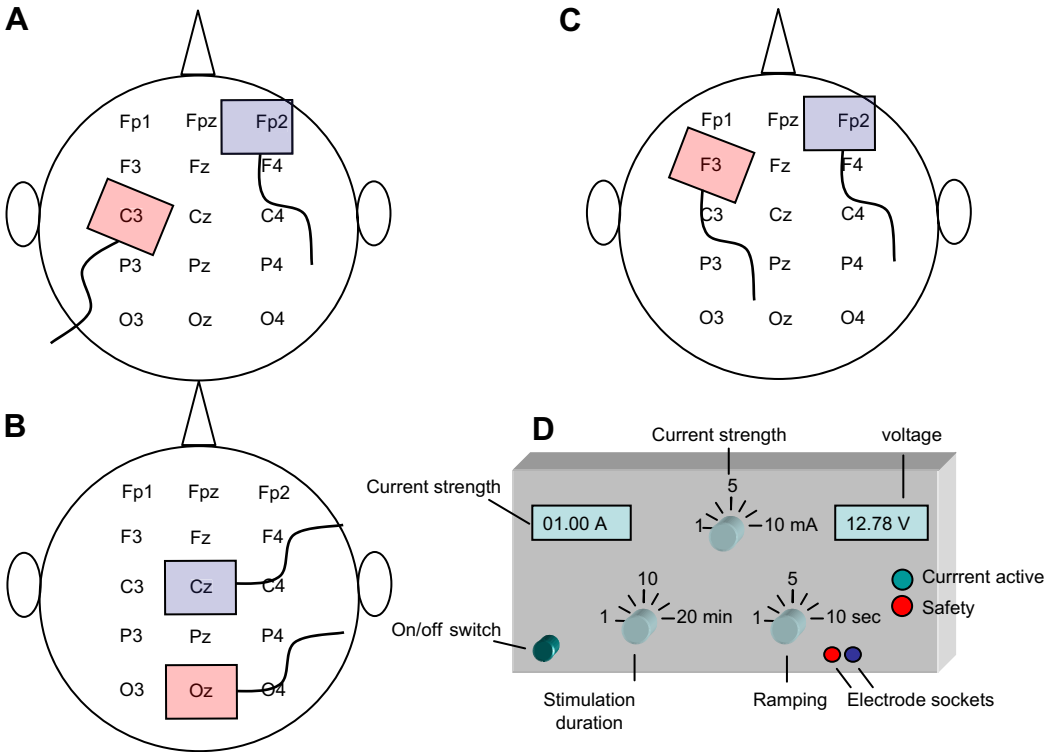

Figure 1 Principle features of tDCS. Schematic drawing of electrode positions suited for tDCS of the primary motor cortex (**A**), the visual cortex (**B**), the dorsolateral prefrontal cortex (**C**), and features of a DC stimulator. Figures **A**-**C** show anodal (positively charged electrode, red color) stimulation of the respective cortices according to the 10-20 system. The cathode (blue color) is positioned such that the resulting current flow (from the cathode to the anode) allows an effective modulation of neuronal excitability under the anode. Note that the term reference electrode (the cathode in these examples) does not mean necessarily that this electrode is functionally inert, but that neuronal excitability changes under this electrode are beyond of the scope of interest with regard to a specific experimental setting. The electrodes are connected to a constant current DC stimulator (**D**). The stimulator should be able to deliver different current intensities (for example, between 1-10 mA), different stimulation durations, and a ramp switch at the beginning and end of stimulation, to allow for protocols inducing short- as well as long-lasting effects of tDCS and to diminish perceptions at the begin and end of stimulation. Current intensity and voltage are controlled online during stimulation. If the voltage needed to deliver a defined current strength is too large because of high resistance, a safety function is activated that terminates stimulation.

tDCS, such as headache, dizziness, nausea, and an itching sensation as well as skin irritation under the electrodes.[34] Specifically, electrodes above the mastoids, which are used for galvanic stimulation of the vestibular system, might induce nausea.[51] Because tDCS neither causes epileptic seizures nor reduces the seizure threshold in animals,[52] seizures do not appear to be a risk for healthy subjects. However, this may not be true for patients with epilepsy.

The safety of stimulation protocols for patients is also important. In general, the precautions that apply are similar to those discussed previously. However, when protocols containing stimulation parameters significantly more intense than those in current use are used, safety measures (for example, cognitive tests, EEG, MRI, markers of neuronal damage, questionnaires asking for side effects, and clinical symptoms) should be undertaken. This is especially important because the altered physiology in neuropsychiatric diseases might render the brain more vulnerable to adverse effects.

Because relatively strong tDCS protocols might be used in clinical studies, safety measures should be added to exclude deleterious effects of tDCS, which might be related to disease-specific damage of brain tissue, if the stimulation protocol is significantly stronger than what has been previously tested.

Conclusions

tDCS has been reintroduced as a noninvasive tool to guide neuroplasticity and modulate cortical function by tonic stimulation with weak direct currents. The aim of this article is to propose guidelines on how to perform tDCS safely and effectively. Because many laboratories have just started using this technique, it is necessary to stratify stimulation protocols to enhance comparability of research results. However, it is also important to underscore that tDCS research is in its early stages and therefore future studies might change some of the current concepts.

Some of the topics presented here were discussed at the first tDCS club workshop held in Milan in March 2008, supported by Università di Milano, Fondazione IRCCS Opsedale Maggiore Policlinico, Mangiagalli e Regina Elena, Associazione Amici del Centro Dino Ferrari Milano, Italy. We thank Ms. Devee Schoenberg of the NINDS for expert editing of the manuscript.

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