Practical Guide to Transcranial Direct Current Stimulation

Principles, Procedures and Applications

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Foreword

This is the most comprehensive book on the subject of transcranial direct current stimulation (tDCS) yet written. Its editors and authors are some of the most accomplished scientists in their fields. They are intelligent, hardworking, and passionate about their research in a way that helps them to succeed where others fail. Few of them started their careers focused on tDCS, but came to it through a variety of avenues: engineering, electronics, psychology, neuroscience, medicine, and others. All have found through the course of their professions that brain stimulation, and tDCS in particular, might fill a niche that has been lacking until now.

Over the last decade, brain stimulation has undergone extraordinary growth for the study of the healthy human brain and for the study and treatment of brain and mental illness. In terms of brain stimulation, tDCS is becoming the most widespread method. Many advantages of tDCS have helped to fuel this growth. Its most basic requirements are a source of controlled current and electrodes that can be temporarily fixed to the body. Compared with most other methods of stimulation, and pharmaceuticals, this makes tDCS technically simpler and much less expensive to administer. Also, as we can find in this book, it appears to be safe. This combination of low cost, simplicity, and safety has generated a lot of interest in tDCS. The many potential advantages of tDCS have driven efforts to increase its efficacy, without which tDCS is useless. These ongoing attempts are described here with great detail.

The increasing use of tDCS has allowed for the testing of hypotheses regarding the brain basis of cognition and behavior that could not be studied in healthy humans until its development. One of these is how changes in behavior are associated with changes in activity of specific brain regions and networks. If a brain region supports a specific behavior, or patterns of behavior, then increasing or decreasing activity in that region should influence that behavior. tDCS applied to a brain region may facilitate brain states that improve (or suppress) different forms of cognition, such as learning, memory, attention, or perception. Many studies described in this book have shown alterations in these forms of cognition using tDCS applied to brain areas suspected of being involved in these forms of cognition and others that have failed. tDCS offers another line of evidence as to how brain areas are involved in

these cognitive processes. In addition, once identified, tDCS-based methods could be used to enhance cognition for real-world purposes. Effective and reliable methods for cognitive enhancement based on tDCS could lead to many benefits in neuroergonomics, which is the use of our understanding of the mind and brain to enhance work and technology, along with a variety of other endeavors including education, science, sports, music, and art. Indeed, all areas of human endeavor could benefit from a reliable method of altering cognition.

In addition, it offers hope for new forms of treatment that could reduce suffering for the many millions of patients with clinical disorders who are currently not helped or are even being hindered by available medical treatments. Those suffering from disorders such as addiction, depression, anxiety, psychosis, chronic pain, traumatic brain injury, stroke, dementia, and many others have a need for medical solutions that are safer, more effective, and more economical than what is currently available. The huge physical, emotional, and economic drain on society makes it imperative that we leave no stone unturned in looking for answers. tDCS offers us at least a chance to reduce this suffering. Many of the latest advances using tDCS to reduce the impact of these disorders are described in this book. There is definite progress in improving the ability of tDCS to help fight these disorders.

At the same time, tDCS has suffered many problems often associated with new technologies. Early successes lead to exuberance and high expectations for the technology's future potential. Eventually though, some early results cannot be replicated in subsequent studies, inexperienced users make mistakes that complicate the literature, and the hype associated with a few early successes does not play out. This can turn into indifference and even resentment on the part of the media and broader scientific community, stifling funding and publications needed for potentially important and useful research. In addition, if one considers the vast number of ways that tDCS can be applied, and the even larger number of ways that electric current can be modulated in time, it can be concluded that a nearly infinite variety of methods for applying TES are available. A single unsuccessful attempt is often described as a "failure of tDCS." However, one failed attempt leaves many millions of alternatives yet untried, with those that succeed still waiting to be discovered.

Finding new successes for tDCS is a large focus of this book. Methods to optimize tDCS effects described here include modeling of current pathways combined with neuroimaging of individual differences in brain structure and organization, leading to individualized electrode montages. Optimization of more general experimental procedures across laboratories is also called for. A large variety of methods, which vary in current intensity, density, and duration, electrode types, methods of electrode placement, sham control, and blinding procedures, can be found in the studies described throughout this book. While beneficial in terms of discovery (e.g., one method may result in a new discovery, while another equally valid method does not for some reason), this makes it very difficult to compare across studies and laboratories. Such problems contribute to the perceived lack of replication in the field, but this may result from procedural differences across studies, with few "true" replications actually being performed.

While this book has much to say about the success stories of tDCS, and hope for its future, this is not hype. It relates the hard science of what tDCS is about and its limitations. Its main points regarding the technical and experimental underpinnings of tDCS research are meant to inform, not inflame, and to give the reader a sense of the underlying reality of this method, at least as it is understood today. The reader will undoubtedly come away with a much better grasp of the current status of this dynamic and still expanding field, along with many questions. One of these is: What is the full description of the effects of tDCS at each level of the nervous system? tDCS interacts with the nervous system at every level, from the molecular up through to the systems and gross anatomical levels, with both neurons and glia, all to different degrees depending on their physical properties and the exact tDCS protocol used. Some of these interactions may also vary minute by minute as tDCS progresses. As with pharmaceuticals, it is impossible to know for sure if we have captured every point of interaction between a treatment and the human body and every aspect of this very complex process. Chances are good that we are missing something with an important influence on brain and behavior. Only further study can help to answer these questions.

From its beginning, tDCS has pointed out many flaws and inadequacies in our understanding of the nervous system. How could this low a level of current cross the skull and enter the brain? When action potential threshold is 10–20 mV above resting potential for a typical neuron, how could a change of 0.5 mV or less have any effect? Uncertainty regarding mechanisms such as these leaves many other details of tDCS uncertain. What is the spatial resolution of tDCS? That is, how far can an electrode be moved while still producing similar results within an individual? Most importantly, what is the tDCS electrode size and placement and stimulation polarity, amplitude, and duration that will produce the best results for a given application?

As with most areas of science, there is no real end to this process of discovery. Along the way, we may find a few nuggets of truth that stand up to further study, and many more questions will arise. With so many people around the world lacking safe and effective medical care, the hope is that this work will lead to new forms of treatment that will help to reduce their suffering. The ultimate goal of all science is to increase our understanding of the world around us and to use this in order to help give people a better quality of life that is less burdened by suffering and despair. This effort, and the hope behind it, is what shines through this book most of all.

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Preface

The field of brain stimulation has enormously expanded over the past decades. Technological progress in biomedical and engineering sciences facilitated advances in understanding physiological and pathological neural dynamics in the central nervous system that represent functional targets for brain stimulation and mechanisms that underlie the brain stimulation effects.

Among specific techniques of noninvasive stimulation, transcranial direct current stimulation (tDCS) has gained steadily growing interest by scientists, clinicians, and the public. This is not surprising, as tDCS research can facilitate insight into neurophysiological mechanisms underlying the development and maintenance of difficult-to-treat disorders and symptoms, as well as provide insight into the linkage between neurophysiological characteristics of neural networks and functional and behavioral outcomes. Further, aiming for enduring alterations of neuronal activity, tDCS bears enormous clinical potential in a broad range of medical disciplines, such as neurology, psychiatry, pain management, or neurorehabilitation, because pathological changes in neural activity are common in many diseases and neurostimulation techniques can be employed to attempt functional normalization of the neural circuitry.

Hand in hand with growing interest in tDCS, new questions and challenges have emerged, and a need for tDCS professional education and training has tremendously expanded. This *Practical Guide to Transcranial Direct Current Stimulation* is the first comprehensive textbook for tDCS; it provides an overview and in-depth discussion of principles, mechanisms, procedures, and applications of tDCS, as well as methodological considerations, ethics, and professional conduct pertaining to this technique. We hope that this book helps bridge the existing gap in tDCS instructional materials for those who engage in research or clinical applications of this promising technique.

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Abbreviations

ABD	Abduction
ACC	Anterior cingulate cortex
ACh	Acetylcholine
AC-PC	Anterior commissure-posterior commissure
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive subscale
Add	Adduction
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
ADL	Activities of daily living
ADM	Abductor digiti minimi muscle
AEP	Auditory evoked potential
AH	Auditory hallucinations
AHRQ	Agency for Healthcare Research and Quality
AHRS	Auditory Hallucination Rating Scale
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPAR	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AMT	Active motor threshold
AN	Anorexia nervosa
AP	Anteroposterior
AR	Augmented reality
ARAT	Action Research Arm Test
ARS	Autoregressive
ASL	Arterial spin labeling
a-tDCS	Anodal-tDCS
AV	Atrioventricular
BART	Balloon Analog Risk Task
BBT	Box and Block Test
BD	Bipolar disorder
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index

BN	Bulimia nervosa
BOLD	Blood oxygen level dependent
BPA	Brachial plexus avulsion
BP_{ND}	Nondisplaceable binding potential
BOLD-fMRI	Blood oxygen level dependent functional magnetic resonance imaging
bvFTD	Behavioral variant frontotemporal dementia
CAD	Computer-aided design
CCT	Cognitive control therapy
CCQB	Cocaine Craving Questionnaire Brief
CPP	Conditioned place preference
CABG	Coronary artery bypass grafting
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBLP	Chronic leg and back pain
CBP	Chronic back pain
CBS	Corticobasal syndrome
CBT	Cognitive behavioral therapy
CDSS	Calgary Depression Scale in Schizophrenia
CES	Cranial electrotherapy stimulation
CET	Cranial electrostimulation therapy
CFR	Code of Federal Regulations
CGMP	Current good marketing practice
CM	Corticomotoneuronal or chronic migraine
CM-PF	Center median-parafascicular
CN-NINM	Cranial nerve noninvasive neuromodulation
CNS	Central nervous system
COMT	Catechol-*o*-methyltransferase
CONSORT	Consolidated Standards of Reporting Trials
COP	Center of pressure
CPSP	Central post-stroke pain
CRPS	Complex regional pain syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
c-tDCS	Cathodal-tDCS
CUtLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
CVS	Caloric vestibular stimulation
CW	Continuous wave
CSD	Cortical spreading depression
dACC	Dorsal anterior cingulate cortex
DALY	Disability-adjusted life year
DAT	Dementia–Alzheimer's type
DBS	Deep brain stimulation
DC	Direct current
DCN	Dorsal cochlear nucleus

DCS	Direct current stimulation
DeoxyHb	Deoxygenated hemoglobin
DIY	Do-it-yourself
DLB	Dementia with Lewy bodies
DLF	Dorsolateral funiculus
DLPFC	Dorsolateral prefrontal cortex
dPMC	Dorsal premotor cortex
DPNS	Direct peripheral nerve stimulation
DRG	Dorsal root ganglion
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised
DTI	Diffusion tensor imaging
DTNS	Direct trigeminal nerve stimulation
DW	Diffusion weighted
DWI	Diffusion weighted imaging
EA	Electroanesthesia
ECT	Electroconvulsive therapy
ED	Eating disorder
EEG	Electroencephalography
E-field	Electrical field
EMG	Electromyography
EOG	Electrooculogram
EN	Electronarcosis
ERCP	Endoscopic retrograde cholangiopancreatography
ERN	Error-related negativity
ERP	Event-related potential
ES	Electrosleep
EST	Electroshock therapy
EU	European Union
FBBS	Failed back surgery syndrome
FCS	Fronto-cingulo-striatal
FD	Frequency domain
FDI	First dorsal interosseous muscle
FDA	US Food and Drug Administration
FE	Finite element
FEA	Finite element analysis
FEM	Finite element method
FEAST	Focal electrically administered seizure therapy
FES	Functional electrical stimulation
FISSFO	Fade in, short stimulation, fade out
FM	Fibromyalgia
FMA	Fugl-Meyer Assessment
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
FTD	Frontotemporal dementia

GABA	Gamma-aminobutyric acid
GBD	Global Burden of Disease
GMI	Graded motor imagery
GUI	Graphical user interface
GVS	Galvanic vestibular stimulation
HC	Healthy controls
HD	High definition
HD-tDCS	High-definition transcranial direct current stimulation
HFO	High-frequency oscillation
HHb	Deoxy-hemoglobin
HRV	Heart rate variability
IASP	International Association for the Study of Pain
IBS	Irritable bowel syndrome
IC	Informed consent
ICA	Independent component analysis
ICD	Implantable cardioverter defibrillator
iCNES	Invasive cranial nerve electrical stimulation
ICS	Invasive cortical stimulation
IDE	Investigational device exemption
IF	Integrate-and-fire
IHI	Interhemispheric inhibition
IPG	Internal pulse generator
IS	Interferential stimulation
IVR	Immersive virtual reality
IEC	International Electrotechnical Commission
IPG	Implantable pulse generator
IRB	Institutional review board
JTT	Jebsen Taylor test
KVIQ	Kinesthetic and Visual Imagery Questionnaire
KVIQ10	Kinesthetic and Visual Imagery Questionnaire – short version
LDLPFC	Left dorsolateral prefrontal cortex
LEP	Laser evoked potential
LIF	Leaky integrate-and-fire
LFMS	Low-field magnetic stimulation
LFO	Low-frequency oscillations
LLP	Late positive potential
lLLP	Later part of LLP
LPFC	Lateral prefrontal cortex
LM	Lateromedial
LTD	Long-term depression
LTP	Long-term potentiation
L-VGCC	L-type voltage-gated calcium channel
mBLL	Modified Beer-Lambert law
MC	Monte-Carlo
MCBB	MATRICS Consensus Cognitive Battery

MCI	Mild cognitive impairment
MCS	Motor cortex stimulation
MDD	Medical Devices Directive
MEP	Motor evoked potential
MER	Microelectrode recording
MET	Microcurrent electrical therapy
MFC	Medial-frontal cortex
MHC	Multilayer hydrogel composite
MI	Motor imagery
MIDAS	Migraine Disability Assessment
MIQ	Movement Imagery Questionnaire
MIQ-R	Movement Imagery Questionnaire-Revised
MIQ-RS	Movement Imagery Questionnaire-Revised, Second Edition
MIT	Melodic intonation therapy
MNI	Montreal Neurological Institute
MMN	Mismatch negativity
mPFC	Medial prefrontal cortex
MR	Magnetic resonance
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MRSI	Magnetic resonance spectroscopic imaging
MS	Multiple sclerosis
MSO	Maximal stimulator output
MST	Magnetic seizure therapy
MUNE	Motor unit number estimation
NAc	Nucleus accumbens
NE	Noradrenergic
NET	Neuroelectric therapy
NFT	Neurofibrillary tangles
NHS	National Health System
NIBS	Noninvasive brain stimulation
NIMH	National Institute of Mental Health
NIR	Near-infrared
NIRS	Near-infrared spectroscopy
NMDA	*N*-Methyl-D-aspartate
NMDAR	*N*-Methyl-D-aspartate receptor
NOS	Nitric oxide synthase
NPS	Neuropathic Pain Scale
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drug
NVC	Neurovascular coupling
NVU	Neurovascular unit
O2Hb	Oxy-hemoglobin
OCD	Obsessive-compulsive disorder

ONS	Optic nerve stimulation
OR	Operating room
OT	Occupational therapy
o-tDCS	Oscillating-tDCS
PA	Prism adaptation
PACU	Postanesthesia care unit
PAG	Periaqueductal grey
PCA	Patient-controlled analgesia
PD	Parkinson's disease
PANSS	Positive and Negative Syndrome Scale
PENS	Percutaneous electrical nerve stimulation
PET	Positron emission tomography
PGE2	Prostaglandin E2
PI	Principal investigator
PLP	Phantom limb pain
PMR	Percutaneous laser myocardial revascularization
PNS	Peripheral nerve stimulation
PNFS	Peripheral nerve field stimulation
PPA	Primary progressive aphasia
PPC	Posterior parietal cortex
POMS	Profile of Mood States
PPF	Paired-pulse facilitation
PROCESS	Prospective Randomized Controlled Multicenter Trial on the Effectiveness of Spinal Cord Stimulation
PSN	Primary sensory neurons
PSP	Post-stroke pain
PSTH	Peristimulus time histogram
PSYRATS	Psychotic Symptom Rating Scales
preSMA	Pre-supplementary motor area
PT	Physical therapy
PVA	Polyvinyl alcohol
PVG	Periventricular grey
RAGT	Robot-assisted gait training
rCBF	Regional cerebral blood flow
RCT	Randomized controlled trial
RF	Radiofrequency
rIFC	Right inferior frontal cortex
rIFG	Right inferior frontal gyrus
RM	Receptor-mediated neurotransmission
ROI	Region of interest
RS	Remotely supervised
rsfMRI	Resting state functional magnetic resonance imaging
RSN	Resting state network
rTMS	Repetitive transcranial magnetic stimulation
Rx	Receivers

S1	Somatosensory
SAI	Short-latency afferent inhibition
SEP	Somatosensory evoked potential
SAE	Serious adverse event
SANS	Scale for the Assessment of Negative Symptoms
SCS	Spinal cord stimulation
SD	Source-detector
SDMT	Symbol Digit Modalities Test
SE	Standard error
SEF	Somatosensory evoked magnetic field
SEM	Standard error of means
SERT	Serotonin reuptake transporter
SFS	Simple finger sequence
SICI	Short-interval intracortical inhibition
SLM	Left superior temporal gyrus
SMA	Supplementary motor area
SNRI	selective norepinephrine reuptake inhibitors
so-tDCS	Slow oscillating-tDCS
SPA	Stimulation-produced analgesia
SPECT	Single photon emission computed tomography
SRT	Simple reaction time
SST	Stop-signal task
SSRI	Selective serotonin reuptake inhibitors
STAR*-D	Sequenced Treatment Alternatives to Relieve Depression
STN	Subthalamic nucleus
SUNCT	Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing
T	Tesla
TD	Time domain
ts-DCS	Transspinal direct current stimulation
TDMI	Time-Dependent Motor Imagery Screening Test
TEM	Treatment-emergent (hypo)mania
TKA	Total knee arthroplasty
TRD	Treatment-resistant depression
tSMS	Transcranial static magnetic stimulation
tACS	Transcranial alternating current stimulation
TBS	Theta burst stimulation
TCES	Transcutaneous cranial electrical stimulation
TCET	Transcerebral electrotherapy
TCMP	Transcranial micropolarization
$tcPO_2$	Transcutaneous oxygen pressure
tDCS	Transcranial direct current stimulation
TEM	Treatment-emergent hypomania/mania
tES	Transcranial electrical stimulation
TENS	Transcutaneous electrical nerve stimulation

TMS	Transcranial magnetic stimulation
TNP	Trigeminal neuropathic pain
TNS	Trigeminal nerve stimulation
tPCS	Transcranial pulsed current stimulation
tRNS	Transcranial random noise stimulation
TSCS	Transcutaneous spinal cord stimulation
TUS	Transcranial ultrasound
Tx	Transmitters
UNODC	United Nations Office on Drugs and Crime
UPDRS	Unified Parkinson's Disease Rating Scale
VAS	Visual Analogue Scale
vmPFC	Ventro-medial prefrontal cortex
VEP	Visual-evoked potential
VDCC	Voltage dependent calcium channel
VGNC	Voltage gated sodium channel
VOI	Volume of interest
VMIQ	Vividness of Movement Imagery Questionnaire
VPM	Ventroposteromedial
VMR	Vasomotor reactivity
VNS	Vagus nerve stimulation
VPL	Ventroposterolateral
VR	Virtual reality
VTA	Ventral tegmental area
WDR	Wide dynamic range
WECS	Within Electrode Current Steering
WHO	World Health Organization
WM	White matter
3D	Three-dimensional
YLD	Years lived with disability

Contents

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Part III Clinical Potential and Applications

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Part I
Basic Aspects: Principles, Mechanisms, Approaches

Chapter 1
Transcranial Direct Current Stimulation Among Technologies for Low-Intensity Transcranial Electrical Stimulation: Classification, History, and Terminology

Nigel Gebodh, Zeinab Esmaeilpour, Devin Adair, Pedro Schestattsky, Felipe Fregni, and Marom Bikson

Classification of tDCS Among Other Brain Stimulation Techniques

Classification of tDCS Among Techniques

The field of brain stimulation dates to the discovery of electrical phenomena, which is not surprising given that human and animal responses to electrical shock are among the earliest evidence for the existence of electricity (Bischoff 1801; Galvani and Aldini 1792; Volta 1800). Research and human trials on electrical brain stimulation, and underling bioelectric phenomena, has been continuous. Modern brain stimulation as a field has branched and evolved into many different categories of devices and tech-

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niques, but whose commonality remains to alter brain or specific nervous system functions by introducing electrical currents through electricity or magnetism. The contemporary landscape of stimulation techniques covers a vast expanse of applications and nomenclatures, many with overlapping aspects. An introduction to tDCS should therefore place it among this landscape of brain stimulation techniques. This includes presenting a simplified mapping and categorization of selected historical and contemporary stimulation techniques and showing how they are categorically interrelated. This by no means should be taken as a complete assortment of stimulation techniques (Guleyupoglu et al. 2013), but rather to clarify the unique features and historical role of tDCS in modern neuromodulation.

When it comes to the categorizing methods of stimulation, several different approaches can be taken. A first simple arrangement is to group stimulation methods into invasive and non-invasive procedures (Fig. 1.1). At this level of division, the obvious distinction lies in the placement of stimulating electrodes. Invasive brain stimulation techniques involve patients undergoing anesthesia or receiving analgesics and having stimulating electrodes surgical implanted in specified regions of the brain, spinal cord, subcutaneously, or around nerves. These implanted electrodes are then activated and used to deliver electrical stimulation to specific regions of the brain, the spinal cord, or specific nerves. Primary stimulation targets are considered local and adjacent to implanted electrodes (McIntyre et al. 2004). Noninvasive techniques, on the other hand, involves the external placement of electrodes (or magnetic coils) without breaking the skin or entering the body cavity, and do not require surgical procedures for application. These noninvasive electrodes or stimulation apparatuses are placed on areas like the scalp, forehead, or shoulders, though which electricity or magnetism is then delivered. Regions that are influenced by stimulation depend on both the electrode montage and individual anatomy (Dmochowski et al. 2011).

Both invasive and noninvasive categorizations can be further divided into techniques intended to either stimulate the brain (transcranial or intracranial) and those techniques targeting extra-cranial structures (non-transcranial or non-intracranial). For non-invasive brain stimulation (NIBS), transcranial encompasses stimulation techniques that intend to pass electricity, magnetism, or sound through the skull and have specific sub-cranial brain (cortical) targets, whereas non-transcranial encompasses delivering current to extra-cranial targets and thus having non-cortical targets. For invasive brain stimulation (IBS), intracranial techniques include deep brain stimulation (DBS), which targets but is not exclusive to specific limbic, basal ganglia, and thalamic brain areas. Non-intracranial IBS techniques include implants such spinal cord stimulation (SCS) – used to treat chronic pain – (Cameron 2004) and direct peripheral nerve stimulation (DPNS) that involves the implantation of an electrode on a nerve (Oh et al. 2004). Other examples of non-intracranial IBS techniques include invasive cranial nerve electrical stimulation (iCNES) techniques. Some iCNES techniques include vestibular prostheses (VP; Golub et al. 2014); optic nerve stimulation (ONS), used for the restoration of vision (Brelen et al. 2010); vagus nerve stimulation (VNS), first approved by the FDA to treat epilepsy (Beekwilder and Beems 2010); and direct trigeminal nerve stimulation (DTNS), which involves implanting electrode cuffs or arrays directly on a nerve (Slavin et al. 2006). In terms

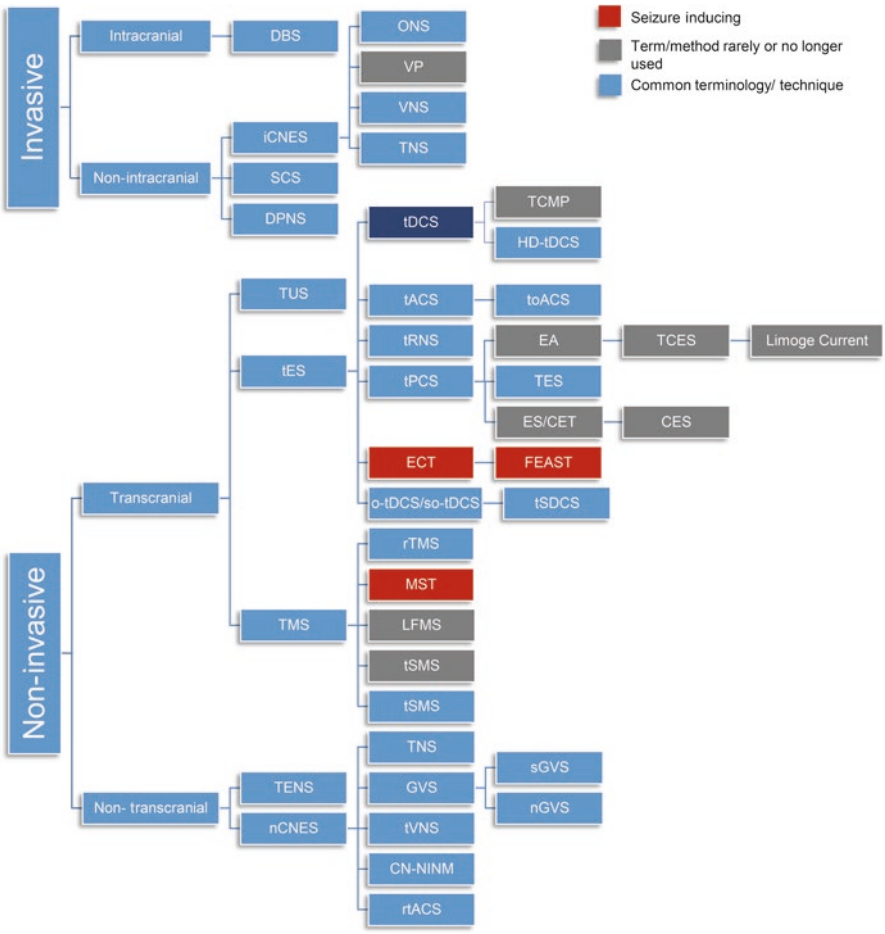

Fig. 1.1 Arrangement of stimulation techniques with common terminology (light blue), terms and methods that are rarely or no longer used (gray), and highlights of seizure-inducing techniques (red). tDCS is highlighted (dark blue) to show its place among the selected techniques

of noninvasive brain stimulation (NIBS) that targets sub-cranial regions, techniques can involve the use of electrical stimulation through electrodes on the scalp, magnetic stimulation with a coil near the scalp, or stimulation with ultrasonic sound through an ultrasound transducer placed on the scalp. Thus, NIBS with transcranial targets is divided into the broad categories of transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES), and the emerging field of transcranial ultrasound (TUS) modulation (Fig. 1.1; Legon et al. 2014).

Non-transcranial electrical stimulation techniques include transcutaneous electrical nerve stimulation (TENS; Robertson et al. 2006), and noninvasive cranial nerve electrical stimulation (nCNES); both of which utilize electrical currents to stimulate nerves. TENS targets all peripheral nerves, whereas nCNES techniques specifically target cranial nerves. nCNES can be subdivided into repetitive transorbital alternative

current stimulation (rtACS; Gall et al. 2010; Bola et al. 2014), trigeminal nerve stimulation (TNS; DeGiorgio et al. 2011; Schoenen et al. 2013), galvanic vestibular stimulation (GVS; Fitzpatrick and Day 2004), transcutaneous vagus nerve stimulation (tVNS; Frangos et al. 2015; Hein et al. 2013; Kraus et al. 2013), and cranial nerve noninvasive neuromodulation (CN-NINM; Danilov et al. 2014). As the name implies, GVS is historically applied using direct current, however with different vestibular targets emerging, the technique has expanded to include stochastic/noisy GVS (Samoudi et al. 2012; Yamamoto et al. 2005) and sinusoidal GVS (Coats 1972).

TMS techniques' main distinction from tES is the use magnetic coils to induce electrical current in the brain (George and Aston-Jones 2010). TMS can be sub-categorized to include repetitive TMS (rTMS; Lefaucheur et al. 2014), seizure-inducing magnetic seizure therapy (MST; Kayser et al. 2015; Lisanby et al. 2003), and the relatively new transcranial static magnetic stimulation (tSMS; Gonzalez-Rosa et al. 2015) and low-field magnetic stimulation (LFMS; Rohan et al. 2004).

Transcranial electrical stimulation approaches pass electrical current directly to the brain via electrodes on the head (Paulus et al. 2013). These techniques include tDCS, transcranial alternating current stimulation (tACS; Antal and Paulus 2013), transcranial random noise stimulation (tRNS; Terney et al. 2008), transcranial pulsed current stimulation (tPCS; Morales-Quezada et al. 2015; Fitzgerald 2014), oscillating tDCS (o-tDCS D'Atri et al. 2015) or sinusoidal oscillating tDCS (so-tDCS; Eggert et al. 2013), and seizure-inducing electroconvulsive therapy (ECT) with the subset, focal electrically administered seizure therapy (FEAST; Spellman et al. 2009). The o-tDCS /so-tdcs technique can further be broken down to include transcranial sinusoidal stimulation (tSDCS). On the other hand, tPCS can be further broken down into "TES", a supra threshold form of tPCS (Kalkman et al. 1992; Zentner et al. 1989); transcutaneous cranial electrical stimulation (TCES; Limoge et al. 1999), a derivative of electroanesthesia (EA; Smith et al. 1967; Wilson et al. 1968) which can include high frequency currents (Limoge et al. 1999); and cranial electrotherapy stimulation (CES; Schmitt et al. 1986), which was derived from electrosleep (ES; Dimitrov and Ralev 2015) and later called cranial electro-stimulation therapy (CET; Knutson et al. 1956). Though ECT can also involve the use of pulsed waveforms, it involves unique stimulation schemes, and is not a tPCS subcategory here.

tDCS, like other techniques, is associated with derivative nomenclature and variants. These variants are rooted in the same principles of tDCS (delivering direct current across the head); however, they both take different approaches to how direct current is delivered. For instance, High Definition-tDCS (HD-tDCS) aims to focalize current distribution across the brain so that specific regions are better targeted. There are numerous montage variations of HD-tDCS (Borckardt et al. 2012; Dmochowski et al. 2011; Kuo et al. 2013; Nikolin et al. 2015) including the most common 4 × 1 HD-tDCS montage (Alam et al. 2016; Datta et al. 2009; Hill et al. 2017; Shekhawat et al. 2015; Shen et al. 2016). Another tDCS derivative is transcranial micropolarization (TCMP), which aims to deliver current intensities (700–1000 μA) on that are much less than conventional tDCS (Ilyukhina et al. 2005; Shelyakin et al. 1998). Other terminology associated with tDCS exists, such as

"anodal/cathodal tDCS" or "lateralized" montages, however these are descriptive of the intended outcome of stimulation and not necessarily distinct technique categories (see below).

The fundamental distinction between tDCS and other categorizations of tES is the waveform delivered to the brain during stimulation (Fig. 1.2). tDCS is the only class of neuromodulation technique that delivers a sustained direct current (DC). Almost all other techniques (and essentially all invasive and magnetic techniques) use pulsed stimulation (such as tPCS) while other non-invasive variants include AC waveforms (such as tACS) or random noise (such as tRNS). Thus, the use of a sustained direct current is a characteristic feature of tDCS, and one that should be kept in mind when considering any unique neurophysiologic, cognitive, or behavioral outcomes.

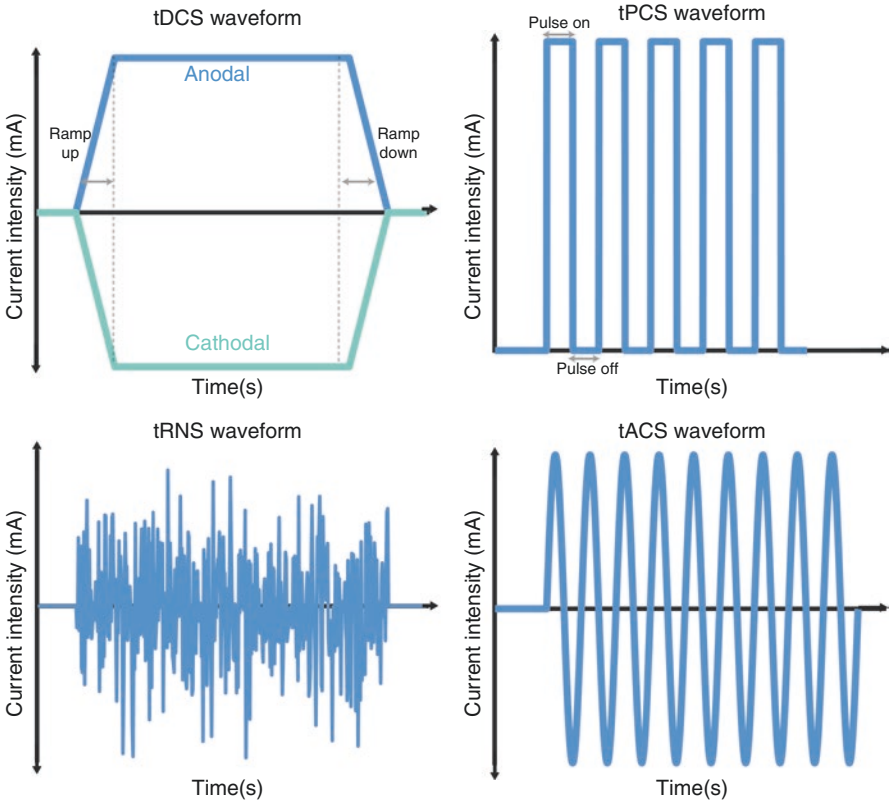

Fig. 1.2 Waveforms of different tES techniques. The tDCS waveform is shown for anodal (blue) and cathodal (light blue) electrodes, which must always be active concurrently. Typically, the current is increased to or ramped up to the desired current intensity and when said intensity is reached the current intensity is held at that level for the duration of stimulation. The tACS waveform shows a typical oscillatory current delivery between electrodes. The tRNS waveform shows a generalized random noise current intensity being delivered during stimulation. The tPCS waveform shows a generalized pulse train of current. Here the duration of pulse on and pulse off time can vary depending on the type of tPCS being done

The Case for Simplicity of tDCS

Direct current represents the most simplistic waveform – though this does not preclude tDCS from producing unique and profound neuromodulatory effects that arise from a sustained current. Nonetheless, regarding the development and adoption of tDCS, we propose that this simplicity underpins the unique role of tDCS in the emergence of modern non-invasive neuromodulation and its grounding in science. Decades of modern work have firmly established that direct current stimulation (DCS) changes neuronal excitability and plasticity. To explain the unique role of tDCS in modern neuromodulation, some historical context is necessary.

Direct current was the first form of brain stimulation generated using a device (as opposed to electric fish or static electricity) since it was the simplest to build – connecting a "voltaic pile" (early battery) to the body. Thus, this approach was the earliest example of electrical stimulation in humans and animals (leading to early theories of the role of electricity in physiology). Later, the first demonstration of long term potentiation was made using direct current (Bindman et al. 1964; Gartside 1968; Gartside and Lippold 1967), preceding the well cited studies of Bliss and Lomo (1973). Monophasic pulse stimulation later integrated mechanical methods to rapidly connect and disconnect the DC battery.

The emergence of other stimulation waveforms (e.g. complex pulsed patterns) paralleled development in electronics (Guleyupoglu et al. 2013). For example, the emergence of the microcontroller allowed for the generation of any arbitrary waveform. Enabled by this flexibility, the twentieth century saw the emergence of numerous variations in waveforms, most of which were claimed to be unique and proprietary. The purported uniqueness facilitated marketing of devices but also resulted in reduced transparency of performance. For example, at the end of the twentieth century, devices FDA-cleared for CES each promised a unique waveform (Fig. 1.3). In a sense this uniqueness (exclusivity) impeded clinical research which benefits from uniformity across labs (reproducibility) and transparency. At the turn of the century though, even career researchers in neuromodulation often could not explain the difference in nomenclature (e.g. does electro-sleep use direct current? is CES and CET the same? Guleyupoglu et al. 2013).

In this context, the early work on tDCS that emerged circa 2000 was characterized by (1) high transparency in a simple and reproducible waveform (e.g. 1 mA sustained for 10 min); and (2) a foundation based, not on clinical experience, but on neurophysiological data (e.g. modulation of TMS evoked responses; Fig. 1.4). These two fundamental characteristics, followed by dozens of rigorous human neurophysiology trials (including multiple independent replications) and animal electrophysiology (steming from our own group; Bikson et al. 2004) established the scientific foundation of tDCS. Work on tDCS, in turn, supported a new era in modern NIBS research. For example, modern tACS approaches mimicked tDCS montages, similarly used a basic and well-defined waveform (single sinusoid), and identical neurophysiology markers of response prior to clinical trials. Clinical trials that used tDCS (starting from our group; Fregni 2005; Fregni et al. 2006b) were