CHAPTER

16

Transcranial Electrical Stimulation to Enhance Cognitive Abilities in the Atypically Developing Brain

Beatrix Krause, Chung Yen Looi, and Roi Cohen Kadosh

Department of Experimental Psychology, University of Oxford, Oxford, UK

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INTRODUCTION

Cognitive loss or underdevelopment can cause a chain of severe consequences in an individual's life. Depending on the type and degree of the deficit, school performance may initially be low, but throughout development the external cognitive demands increase and therefore the child starts to lag more and more behind in the educational environment. Moreover, the chances for academic and occupational achievements become further and further reduced, and the rates of unemployment and depression increase (Parsons & Bynner, 2005; Stein, Blum, & Barbaresi, 2011). This downward spiral demonstrates how quality of life can be greatly compromised in individuals with poor cognitive abilities. Societal values, including physical, financial and social wellbeing, play a big role in an individual's quality of life. These factors affect an individual's competence and independence, freedom of choice and perceived situational control, work, leisure activities, education and productivity, and eventually, of course, emotional wellbeing – including satisfaction, self-esteem, status, and respect (Felce & Perry, 1995). In fact, academic achievement, such as childhood reading and mathematical abilities, are strongly linked with socioeconomic status, but also academic motivation, educational duration, and intelligence later at mid-age (i.e., around 40 years) (Ritchie & Bates, 2013).

The impact of academic achievement also stretches beyond the individual level. At the societal level, learning difficulties contribute to a high rate of unemployment. This results in a lack of tax payments and, furthermore, the need to treat the consequences, such as increased rates of obesity and depressive symptoms in affected individuals. In addition, the consequences of learning impairments cause further costs due to increased crime rates and drug abuse, and for special educational training, to remediate these deleterious effects (Gross, Jones, Raby, & Tolfree, 2006; Gross, Hudson, & Price, 2009; Matza, Paramore, & Prasad, 2005). For these reasons, it is pressing to find successful, and more efficient interventions in order to ameliorate learning disabilities and childhood developmental disorders.

Some of the most common types of child behavioral and cognitive developmental impairments are dyslexia, developmental dyscalculia (DD), attention deficit hyperactivity disorder (ADHD), and autism. Each of these is associated with profound cognitive impairments in at least one major domain of cognitive processing, or even combinations of these. The DSM-V states that learning disabilities involve a central nervous system (CNS)-based disorder that affects reading, writing, and/or mathematics, leading to severe underachievement on common psychometric tests that assess the cognitive domain in question. This is despite having an average IQ. However, it also states that such learning disabilities are more complex and require the consideration and evaluation of a range of environmental

influences in order to assess the exact problem (American Psychiatric Association, 2013; Gilger & Kaplan, 2001; Rimrodt & Lipkin, 2011). Accordingly, the exact diagnosis and boundaries between the different types of learning disabilities are difficult, and the large variety of symptoms require different approaches for coping (Stein et al., 2011). There is significant overlap and a variety of comorbidities among different types of disorders, such that cognitive domains (for instance, working memory) are impaired in several different disorders but the general manifestations of the cognitive problems differ (Gilger & Kaplan, 2001; Willcutt et al., 2013). Learning difficulties in developmental disorders are generally associated with abnormalities in the trajectory of brain development, both at the functional and the structural level – examples of which we will discuss in more detail later.

If successful cognitive training is applied during developmental periods of high neural plasticity – i.e., sensitive periods – atypical brain functioning and development can be partially redirected, promoting structural reorganization (Knudsen, 2004). Plasticity is the capacity of the brain to change with experience, and can involve changes in the size or the number of neurons or synapses, the organization or conductivity of white matter connections, or enhanced vascularization (Zatorre, Fields, & Johansen-Berg, 2012). Conventional intervention methods involve individualized cognitive training, including, for example, one-on-one instructions, as well as computerized learning games (see, for instance, Cohen Kadosh, Dowker, Heine, Kaufmann, & Kucian, 2013). There is also a variety of cognitive enhancement methods that are suggested to modulate brain functioning, such as medication (in the case of ADHD, Ritalin™ is the most commonly prescribed drug), yoga and mindfulness meditation, computer training games, and physical exercise (Dresler et al., 2013).

Unfortunately, training cannot always be applied during periods of maximum learning capacity (see Fig. 16.1). It is also important to note that each individual has his or her own limit for cognitive capacity, which can be reached, but not necessarily exceeded, using cognitive training (Jolles & Crone, 2012). As a consequence, the deficit persists and limits the individual's academic success further. Given the importance of an individual's personal circumstances, existing levels of capacity for brain plasticity, and past history of intervention attempts, we need to find more successful interventions that can cater to a variety of deficits. We therefore need to target the neural substrate directly, in addition to the moderate improvement gained from conventional cognitive methods, to overcome the individual barriers of brain plasticity. Non-invasive brain stimulation has been suggested to have the capacity to reopen sensitive periods in developmental disorders (see, for example, Krause & Cohen Kadosh, 2013), by "releasing the brakes" of cortical inhibition (Hensch & Bilimoria, 2012).

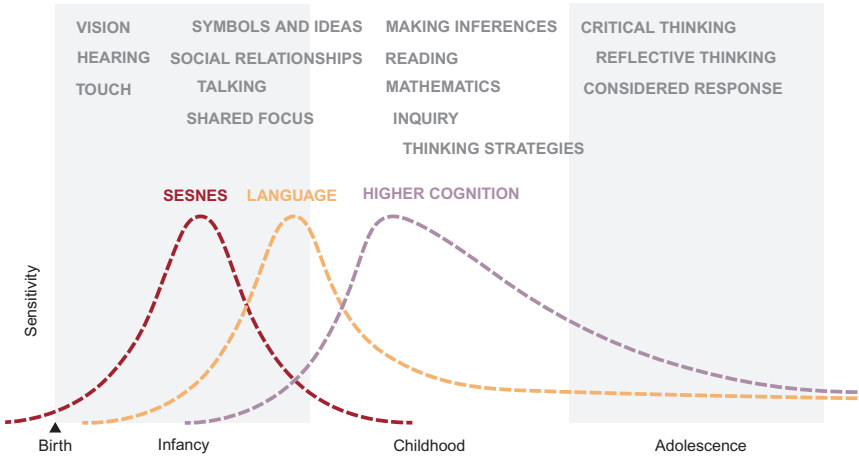

FIGURE 16.1 **The sensitive periods of the cortex for different cognitive functions peak at different time points in child development.** The curves symbolize the degree of sensitivity for learning; the flatter the curve, the less learning capacity the individual holds at a given stage of development. For example, senses develop early on during infancy, whereas language peaks later, and higher-level cognition matures throughout childhood. The differences in peaks must be taken into consideration for tES application. Parameters may need to be carefully adapted to a higher baseline capacity for plasticity, such that potential overstimulation can be avoided. *Figure reproduced from Bardin (2012), by permission from Macmillan Publishers Ltd.*

It has recently been suggested that we can use non-invasive brain stimulation techniques, such as transcranial electrical stimulation (tES), to improve developmental learning and/or behavioral deficits in children. Due to their cortical deficits, cognitive learning impairments that would benefit from such neuroenhancement techniques include, for example, dyslexia, DD, and ADHD (Cohen Kadosh, 2013; Krause & Cohen Kadosh, 2013; Vicario & Nitsche, 2013a). We suggest that a variety of developmental disorders, including autism, Down's syndrome, Williams syndrome, schizophrenia, and motor disorders involving cognitive deficits may also be improved by enhancing brain plasticity using tES in combination with successful behavioral training.

We will discuss these options in the light of implementing tES into pediatrics as a treatment and intervention method. In addition, we will provide an outlook on how tES could be used in a more practical environment: the school classroom. We will further outline important safety and ethical considerations, and present an overview of tES methodologies and its potential applications in this field of neurodevelopmental disorders. Finally, we will elaborate on the biological functioning of the techniques.

FORMS OF tES

As discussed in other chapters in this book (e.g., Chapter 2), tES is a relatively cheap, portable, and easy-to-administer non-invasive stimulation method that can be used to increase brain plasticity. Two or more electrodes are strapped onto the person's scalp surface by rubber bands, or are integrated into a whole-head cap, inducing a weak electrical current into the cortical surface under the electrodes (Im, Park, Shim, Chang, & Kim, 2012). The most frequently used current intensity in cognitive research settings is between 1 and 2 mA. The international or extended 10–20 system for EEG recording is used to localize the desired stimulation site on the individual head (Auvichayapat & Auvichayapat, 2011) (Figure 16.2). In the research setting, a sham condition can be applied, or even preprogrammed, which allows both subject- and experimenter-blinding. In the most commonly used sham condition, the stimulator delivers current for the initial 30 seconds but then ramps down and remains inactive while the participant is engaged in the training. Since skin sensations such as

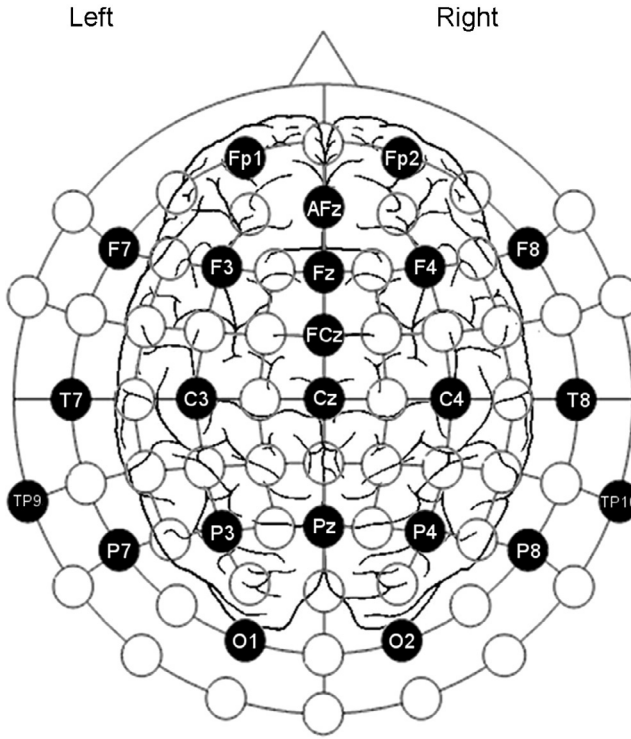

FIGURE 16.2 Electrode positions according to the international 10–20 system for EEG recording, based on the individual's head proportions.

tingling, itching, or a light stinging can occur during the initial period of the stimulation, the participant is unable to distinguish the real from the sham stimulation (Gandiga, Hummel, & Cohen, 2006).

Four major forms of tES can be distinguished: anodal and cathodal transcranial direct current stimulation (A-tDCS and C-tDCS, respectively), transcranial random noise stimulation (tRNS), and transcranial alternating current stimulation (tACS). In tDCS, the current flows from the anode to the cathode and thereby is likely to induce neuronal excitability under the anode (Nitsche & Paulus, 2001) and reductions in excitability under the cathode (Nitsche et al., 2003). In particular, A-tDCS usually leads to depolarization of neurons, whereas C-tDCS causes hyperpolarization, and therefore the inhibition of firing (Nitsche & Paulus, 2000). This means that activity can be enhanced in one area while reduced in another. An alternative approach is to stimulate (A-tDCS) one region and place the cathode over a neutral region on the scalp or the body, in order to affect only a single region. Such a neutral position can be the vertex or the forehead above the eyes, termed the supraorbital region (DaSilva, Volz, Bikson, & Fregni, 2011). Alternatively, some studies use the shoulder (deltoid muscle), the cheek (buccinator muscle), or the chin as a reference (Im et al., 2012). The choice of the placement of the reference electrode, however, affects the induced excitability under the stimulation electrode and may therefore have to be adjusted for the distance between the two electrodes (Moliadze, Antal, & Paulus, 2010).

tRNS induces current noise (e.g., high frequencies between 100 and 600 Hz) at a certain current intensity (e.g., 1.5 mA), and thereby enhances cortical excitability (Terney, Chaieb, Moliadze, Antal, & Paulus, 2008). The output from both electrodes is thus polarity unspecific, and the user can stimulate two regions at the same time – such as bilateral homologs in the frontal cortex. This method has been shown to have superior effects to A-tDCS and C-tDCS in certain cases, but not all (Fertonani, Pirulli, & Miniussi, 2011; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011). tRNS has the advantage of causing less skin sensation, which allows more effective subject-blinding (Ambrus, Paulus, & Antal, 2010). The facilitatory processing effects of tRNS can be observed after just 10 minutes, and can have aftereffects of sustained excitability for at least 60 minutes post-stimulation after a single session (Terney et al., 2008). This electrical noise is hypothesized to increase excitability by a mechanism called "stochastic resonance," in which the noise increases the sensitivity to subthreshold stimuli on a background of ongoing neuronal activity, such that the firing threshold is reached more easily (Fertonani et al., 2011). The neuronal response to weak stimuli is therefore enhanced with the right amount of noise added. Excessive noise intensity however, can invert the enhancement effect and instead impair the neuron's capacity to detect signals amongst the noise (Moss, Ward, & Sannita, 2004).

The mechanism of tACS involves changes in the synchronicity of neurons by inducing sinusoidal wave-like currents in a fixed frequency range (for example, beta frequencies of 14–22 Hz), whereby different frequencies have different effects (Kanai, Chaieb, Antal, Walsh, & Paulus, 2008; Kanai, Paulus, & Walsh, 2010). The effect is based on alterations of the oscillatory pattern of the stimulated neurons (Thut, Miniussi, & Gross, 2012).

The advantage of tES over a similar non-invasive brain stimulation technique, called transcranial magnetic stimulation (TMS), is that it provides a better sham control. tES is not noticeably different from its sham condition (Gandiga et al., 2006), whereas TMS causes loud clicking noises for each administered pulse and, often, muscle twitches under the stimulation focus (Wagner, Valero-Cabre, & Pascual-Leone, 2007). Furthermore, the side effects that may easily identify real stimulation in tES studies are more flexibly manageable. For example, tACS can induce phosphenes, which in turn can be avoided with the right choice of stimulation parameters (for discussion, see Davis, Gold, Pascual-Leone, & Bracewell, 2013).

Previously, an advantage of TMS has been the increased stimulation focality, since electrode sizes for tES commonly start at a surface area of 4×4 cm. However, with the development of high-definition tDCS (HD-tDCS) it is now also possible to achieve more focal effects using tES (Datta, Elwassif, Battaglia, & Bikson, 2008). The disadvantage of this form is that expensive neuronavigation equipment may become necessary in order to localize the exact target stimulation site in each individual. In cases where there is a very focally restrained neurological deficit, this will be beneficial. Aside from the technical flexibility in tES usage, the choice of the stimulation region and the training applied during the sessions are crucial for the outcome of the intervention. We will therefore discuss some of the current applications and issues regarding such choices.

LEARNING AND tES

For successful cognitive processing, a multitude of cognitive subfunctions subserved by different brain areas are required to interact efficiently in order to produce meaningful output. The interaction between brain areas is therefore more important for the behavioral outcome than the efficient processing of a single brain region (Spencer-Smith & Anderson, 2009). Furthermore, the balance between cortical excitation and inhibition (E/I balance) is crucial for the capacity for plastic changes in synaptic connections, and therefore also determines the efficiency of information transfer in the brain (Turrigiano & Nelson, 2000). tES has the potential to modulate activity in whole networks rather than just a single region, and is thought to modulate different brain mechanisms, including E/I (Krause, Marquez-Ruiz, & Cohen Kadosh 2013; Polania, Paulus, Antal, & Nitsche, 2011). These features are highly

useful, given the complexity of abnormalities observed in individuals with learning difficulties, and in order to enhance plasticity and long-term cortical reorganization. Even though in some cases the original source area in the deficient brain circuit might not be accessible to tES (e.g., subcortical regions, such as the thalamus), there is evidence that stimulation of later circuit areas in the processing chain can affect and improve the behavioral or cognitive outcome, even for extended periods of time (Benninger et al., 2010). Ideally, the stimulation will modify the whole network to adapt and function more efficiently.

Long-term potentiation (LTP) refers to the prolonged and enhanced activity between neurons that fire together in a Hebbian fashion. The formation of LTP is crucial for information storage (Turrigiano & Nelson, 2000), and is capable of inducing cortical reorganization (Hess & Donoghue, 1994). LTP only occurs when neurons receive sufficient activation, which is modulated by the excitatory neurotransmitter glutamate (Collingridge & Bliss, 1987). The inhibitory neurotransmitter gamma-aminobutyric acid (GABA) also plays an important role in LTP. GABAergic inhibition is viewed as a gatekeeper for LTP and plasticity processes, and its reduction can contribute to activity-dependent cortical reorganization (Hess & Donoghue, 1994). For example, a decrease in GABAergic inhibition is accompanied by a facilitation in practice-based learning, whereas an increase in GABA is associated with reduced learning effects (Floyer-Lea, Wylezinska, Kincses, & Matthews, 2006; Ziemann, Muellbacher, Hallett, & Cohen, 2001). The change in learning also varies with the degree of change in GABA (Stagg, Bachtiar, & Johansen-Berg, 2011). These neural learning-related functional processes are crucial to those with atypical cortical development. Regional levels of GABA and glutamate – i.e., cortical inhibition and excitation – can be artificially modulated using tES (Clark, Coffman, Trumbo, & Gasparovic, 2011; Stagg et al., 2009). tES can therefore be used to support the restoration of a network in order for it to become more efficient. This also demonstrates the importance of choosing the appropriate training task, as the brain is still required to make the effort to learn. Simultaneously, tES acts as a supporting facilitator and is crucial for the induction of change through the removing of inhibitory restraints (or decreasing facilitation) of the cortex. In the following sections, we will describe some of the methodological and parameter options that have been explored in tES research on cognitive training.

ENHANCING COGNITIVE ABILITIES WITH tES

A wide range of cognitive abilities, but also motor and perceptual functions, have been targeted using different tES methods in adults. Some of the most relevant cognitive abilities affected by childhood atypical

development are working memory, filtering of irrelevant information, attentional processes, reading, speech production, numerical and arithmetic abilities, and also motor learning and visual perception or discrimination (for examples, see Table 16.1). In tES research, experimental tasks that target a highly specific aspect of a cognitive domain are typically used. The cognitive domains targeted are thereby known to be associated with metabolic activity in certain brain areas that are accessible to the stimulation. For example, numerical tasks can range from spatial numerical skills over subitizing or comparing quantities, to counting and computing, which all involve different brain areas to different degrees (Piazza, Mechelli, Butterworth, & Price, 2002). Furthermore, similar types of tasks may engage different brain areas depending on the strategy an individual uses to solve a given problem (Delazer et al., 2005; Rivera, Reiss, Eckert, & Menon, 2005). For example, while some people solve an arithmetic problem by performing the actual computation, another individual might retrieve certain substeps of the calculation from memory. It is therefore important for the optimization of intervention paradigms to combine tES with tasks that tap into the cognitive domain of interest. Importantly, the outcomes should have a meaningful impact on real-life numerical abilities.

A short-term cognitive improvement is of little value in clinical or school settings. What is needed instead is an intervention method that allows for long-term enhancement of cognitive abilities. In addition, it must be noted that the majority of research studies report response times and accuracy separately, and often it is response times in the order of milliseconds that improve, but not necessarily accuracy (see Pascual-Leone, Horvath, & Robertson, 2012). Therefore, depending on the desired outcomes, experimenters should be critical when integrating the latest scientific evidence into the design of more effective intervention programs. Moreover, in the case of a specific learning difficulty – for example, mathematical learning difficulty – it is important to understand that there is often a spectrum of severity, and individuals might differ in their impairments and/or have other co-morbidities, such as ADHD or dyslexia. Therefore, in order to enable successful training with meaningful outcomes for a given individual, these factors should be taken into consideration when designing an intervention. Ideally this will be achieved with the consultation of professionals (e.g., occupational therapists or teachers) who have experience with the previous treatment and impairments of the individual.

Furthermore, in order to achieve the optimal outcome for each individual, important tES methodological considerations involve the number of sessions and intersession intervals, the stimulation parameters (type, polarization, duration, intensity, electrode size, shape and position, frequency if applicable). This is because the resulting dosage and the electric

TABLE 16.1 Common Electrode Positions in Current Brain Stimulation Paradigms*

Electrode Position	Function	Brain Area Targeted	Stimulation	Reference(s)
LANGUAGE				
F3	Vocabulary and syntax	Left DLPFC	A-tDCS (reference contralateral supraorbital)	(Schneider & Hopp, 2011)
FC5	Speech, naming	Left inferior frontal gyrus (IFG)	A-tDCS (reference contralateral supraorbital)	(Holland et al., 2011)
CP5	Word retrieval	Superior temporal gyrus (STG; Wernicke's area)	A-tDCS (reference contralateral supraorbital)	(Fiori et al., 2011)
CP5	Associative language learning	Left posterior perisylvian area (Wernicke's)	A-tDCS (reference contralateral supraorbital)	(Floel, Rosser, Michka, Knecht, & Breitenstein, 2008)
CP5–CP6	Speech	Left superior temporal gyrus (STG; Wernicke's area)	Left-anodal, right-cathodal	(You, Kim, Chun, Jung, & Park, 2011)
T7/TP7–T8/TP8 (extended 10–20 system)	Word reading efficiency	Left posterior temporal cortex	Left-anodal, right-cathodal	(Turkeltaub et al., 2012)
MEMORY				
P3–T5; P6–T4	Word recognition memory and visual attention	Bilateral temporoparietal junctions	A-tDCS	(Ferrucci et al., 2008)
T3–T4	Visual recognition memory	Bilateral temporal lobes	A-tDCS (external reference right deltoid muscle)	(Boggio et al., 2012)
WORKING MEMORY				
F3	3-back task	Left DLPFC	A-tDCS (reference contralateral supraorbital)	(Ohn et al., 2008; Teo, Hoy, Daskalakis, & Fitzgerald, 2011)

TABLE 16.1 Common Electrode Positions in Current Brain Stimulation Paradigms—cont'd

Electrode Position	Function	Brain Area Targeted	Stimulation	Reference(s)
F3	2-back task	Left DLPFC	A-tDCS (reference contralateral supraorbital)	(Mulquiney et al., 2011)
P3–P4	1- and 2-back span task	Posterior parietal cortex	Interaction between task and condition (RALC vs LARC)	(Sandrini, Fertonani, Cohen, & Miniussi, 2012)
P4	Impaired working memory recognition	Left parietal cortex	C-tDCS (reference contralateral cheek)	(Berryhill, Wencil, Branch Coslett, & Olson, 2010)
NUMERICAL ABILITIES				
F3–F4	Arithmetic learning, numerical automaticity	DLPFC	Left-anodal, right-cathodal	(Iuculano & Cohen Kadosh, 2013)
F3–F4	Arithmetic learning	DLPFC	TRNS to bilateral DLPFCs	(Snowball et al., 2013)
P3–P4	Basic numerical skills, numerical learning	Parietal cortex	Left-anodal, right-cathodal	(Iuculano & Cohen Kadosh, 2013)
P3–P4	Basic numerical skills, numerical learning	Parietal cortex	Right-anodal, left-cathodal	(Cohen Kadosh, Soskic, Iuculano, Kanai, & Walsh, 2010)
P3	Mental arithmetic	Left intraparietal sulcus (IPS)	A-tDCS (reference contralateral supraorbital)	(Hauser, Rotzer, Grabner, Merillat, & Jancke, 2013)
P3–P4	Approximate number sense (ANS)	Bilateral parietal lobes	Bilateral tRNS	(Cappelletti et al., 2013)
ATTENTION				
T4/Fz–F8/Cz	Stop-signal task	Right inferior frontal gyrus	A-tDCS (reference contralateral supraorbital)	(Ditye, Jacobson, Walsh, & Lavidor, 2012)

Continued

TABLE 16.1 Common Electrode Positions in Current Brain Stimulation Paradigms—cont'd

Electrode Position	Function	Brain Area Targeted	Stimulation	Reference(s)
P4	Flanker task	Left posterior parietal cortex	C-tDCS to PPC (reference contralateral supraorbital)	(Weiss & Lavidor, 2012)
EXECUTIVE PLANNING				
F3	Tower of London task	Left DLPFC	A-tDCS (reference contralateral supraorbital)	(Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009)
INTELLIGENCE				
F3	Logical reasoning	Left middle frontal gyrus (MFG)	5-Hz tACS (reference vertex)	(Santarnecchi et al., 2013)
T3 (estimated location)	Logical problem solving	Right anterior temporal lobe	A-tDCS (cathode on left anterior temporal lobe)	(Chi & Snyder, 2012)

**Examples of the choice of electrode positions for different types of cognitive tasks that are associated with certain cognitive regions. Note the variety of different cognitive tasks used for similar brain areas.*

field induced in the cortex depend on these and related parameters (Guleyupoglu, Schestatsky, Edwards, Fregni, & Bikson, 2013; Peterchev et al., 2012). It is important to consider that tDCS-induced effects are also affected by individual differences, such as baseline performance, previous educational background, and even personality (see, for example, Berryhill & Jones, 2012; Pena-Gomez, Vidal-Pineiro, Clemente, Pascual-Leone, & Bartres-Faz, 2011; Tseng et al., 2012).

IMPROVING THE DEFICITS: EXAMPLES FOR LEARNING DEFICITS

Developmental cognitive difficulties are associated with atypical structural and functional patterns in the brains of the affected children, compared to typically developing children. This can be demonstrated, for instance in DD (Kucian et al., 2006; Price, Holloway, Rasanen, Vesterinen, & Ansari, 2007; Rykhlevskaia, Uddin, Kondos, & Menon, 2009), dyslexia (Stein & Walsh, 1997; Temple et al., 2003), and ADHD (Shaw et al., 2012). The neurodevelopmental deficits in some of these

developmental disorders are very complex. We will therefore provide some simple results from different meta-analyses based on brain-imaging studies as examples of areas where target-specific tES intervention can be planned and applied.

Developmental Dyscalculia

Developmental dyscalculia refers to the severe difficulty in manipulating numerical information and performing arithmetic operations, which cannot otherwise be explained by cognitive dysfunctions, such as in intelligence, reading, or attention (Butterworth, Varma, & Laurillard, 2011). The usual prevalence of 6–7% (Butterworth et al., 2011) can rise to 26%, when taking into account the existence of several other weaker forms of arithmetic difficulties (Gross-Tsur, Manor, & Shalev, 1996). Individuals with DD usually have a poor prognosis for future employment and socioeconomic status, unless a successful intervention technique can be applied to enhance their performance in the deficient modality (Gabrieli, 2009; Rimrodt & Lipkin, 2011; Stein et al., 2011). tES can be applied to impaired brain areas in order to enhance neural activation during cognitive (i.e., maths or reading) training. It is aimed to restore the abnormalities in structure and functioning to a normalized level, as it can lead to effective and long-lasting intervention effects, and can thereby possibly alter atypical development to typical development if intervention occurs early enough.

The core regions that are associated with DD consist of a wide fronto-parieto-occipital network, with structural abnormalities such as reduced gray matter in bilateral prefrontal and parietal areas, white matter reductions in right temporo-parietal networks, but also decreased functional activation in bilateral intraparietal sulci (IPS) in children during arithmetic tasks (Kucian et al., 2006; Mussolin et al., 2010; Price et al., 2007; Rykhlevskaia et al., 2009). The most consistent functional findings in DD children compared to typically developing children also involve reductions or increases in brain activity in multiple regions compared to typically developing children (Kaufmann, Wood, Rubinsten, & Henik, 2011; see also Table 16.2).

Using tES, the perspective is to enhance excitability in such underactivated areas, while suppressing excitability (i.e., inhibiting) in hyperactive areas. The choice of polarity over the stimulated region depends on the brain state of the receiver, and needs to complement the training methods applied. For example, if a child has very pronounced problems with approximate calculation, the area associated with reduced activity would be the left IPS and the left inferior frontal gyrus (IFG) (Kucian et al., 2006). One of these regions should be chosen as the stimulation site where either anodal tDCS or tRNS can be applied to enhance cortical excitability. Since

TABLE 16.2 Suggested Electrode Positions for Developmental Dyscalculia (DD) According to Neurodevelopmental Deficits*

Underactivation	Overactivation	Electrode Position
Left precuneus		C3–P3
Left IPS		P3
Right inferior parietal lobe		TP4
Left paracentral frontal lobe		C3
Left superior frontal gyrus		F3
Right middle frontal gyrus	Right superior frontal	F4
Left fusiform gyrus		T3
	Postcentral gyri	C3–P3, C4–P4
	Bilateral inferior parietal lobes (including right supramarginal gyrus)	TP3–4
	Paracentral frontal lobes	FCz, Cz

**Brain areas of atypical activation in developmental dyscalculia (DD), according to a meta-analysis of 19 functional MRI papers (Kaufmann et al., 2011). The right column shows approximate electrode positions according to the original 10–20 system for EEG recording (see Homan, Herman, & Purdy, 1987, for these areas to be stimulated by tES). Areas of underactivation are expected to benefit from excitatory stimulation (e.g., anodal tDCS or tRNS), whereas areas of overactivation require inhibitory cathodal tDCS. Electrode positions in the original 10–20 system are called T3, T4, T5, and T6, but have been relabeled as T7, T8, P7, and P8, respectively, in the extended 10–20 system. Measuring the proportions of the head surface provides approximations for the exact location of a cortical area, but since the electrodes are relatively large (typically 16–35 cm^2), the localization in a millimeter range is abundant.*

the atypical activity pattern in this case is mainly restricted to unilateral areas, anodal stimulation to these regions would be possible, with the reference electrode on the contralateral supraorbital area (above the right eye). However, it can be argued that reducing excitability in the same region of the contralateral hemisphere may be beneficial (see Chapter 12). It is therefore a matter of the specific hypothesis underlying the intervention. tRNS would be most applicable in cases where two brain regions, such as bilateral areas, are the stimulation targets (Snowball et al., 2013). The current level of the developmental status of the brain for a given task must be thoroughly assessed for each individual in order to define the appropriate stimulation site. This is crucial especially for children, whose regional recruitment of neural networks differs and changes throughout development (Cohen Kadosh, 2011; Johnson, 2011).

It is important to note here that cognitive loss similar to that observed in developmental disorders (such as DD) might occur through brain damage. For example, acalculia is comparable to DD but is acquired through neurological damage. Acalculia often comes with various comorbidities and deficits in other cognitive domains, as well as neurodegenerative diseases (Boller & Grafman, 1983). The same applies to the other way around: although an intervention design leads to beneficial effects of tES, using the same paradigm in DD may not lead to the same effects. The same applies to other cognitive deficits caused by either brain damage or neurodevelopmental disorders. Even though the symptoms can be similar in both cases, the neurological deficit may be different and will therefore interact differently with tES. This is because various factors, such as the type of damage and its occurrence as a function of age, are different. For example, the flow of the induced current of the stimulation applied to a damaged area is relatively unpredictable, as different tissue types have different properties (Datta, Baker, Bikson, & Fridriksson, 2011; see also Chapter 4).

Dyslexia

Dyslexia has a similar prevalence to dyscalculia and denotes severe difficulties in reading and text comprehension, despite an average IQ (Shaywitz, 2003). Individuals with dyslexia have deficits in fast temporal processing of speech and visual attention, which has been previously associated with an impairment in the magnocellular visual pathway (Stein & Walsh, 1997). Dyslexia has also been associated with reduced levels of activation in temporo-parietal areas, which are generally related to phonological processing and are therefore essential to speech and reading (Gabrieli, 2009; Temple et al., 2003). Reductions in brain activity were found in, for example, the middle temporal gyrus and the inferior and superior temporal gyri, as well as the middle occipital gyrus, compared to normal readers in a study using positron emission tomography (PET) (Paulesu et al., 2001). However, there were no over activations in dyslexic participants compared to control readers. An interesting finding was that, despite investigating groups with different native languages in their respective countries (English, French, and Italian), the pattern of brain activity was slightly different across the groups. The authors interpreted this as a result of different orthographies in the languages, leading to differences in terms of reading difficulty and performance. Furthermore, the observed areas of under-activation in the same subjects were also associated with reduced gray matter volumes, particularly in the inferior temporal cortex (Silani et al., 2005). In this area, the degree of reading impairment was significantly correlated with gray matter volume, such that inferior performance corresponded to higher gray matter density.

Most importantly, however, decreases in gray matter density were observed in the inferior frontal gyrus (IFG) and the middle temporal gyrus, the latter of which was directly adjacent to an area of increased gray matter density – the middle posterior temporal gyrus. These results have important implications for the use of tES. First of all, due to the potential for slight anatomical differences in reading disabilities across languages, the electrode placements have to be determined for each language group separately. The tES training and stimulation design should therefore also be individually adapted, such that the stimulation affects the specific impairment. Secondly, potentially hypoactive or underdeveloped brain areas may lie very close to hyperactive areas, such that larger electrodes may stimulate an area that would preferably be inhibited. Electrode size and positioning must therefore be carefully considered and based on the individual functional anatomy, in order to avoid accidental excitation or suppression of unintended areas. Lastly, the example of the cross-cultural reading study demonstrates that consistently reduced brain activity can largely co-occur with reduced gray matter volume in poor readers compared to normal readers. The subsequent decision to apply excitatory stimulation (e.g., A-tDCS or tRNS) is then made relatively simple and straightforward. The induction of excitability and enhancement of plasticity and LTP would be ideal in this case. However, we should be cautious not to generalize from this to other examples. Different analysis methods and task assessments may affect the interpretation of findings. This is similar in this case, where the stimulation design should be chosen based on the individual's exact reading problem and strong evidence on the associated brain functioning. Experimental data therefore always need to be carefully reviewed to establish the relationship between tasks, activation, and structural abnormalities in learning impairments, and to design a successful intervention strategy.

Some tES studies have successfully improved reading performance by stimulating left temporal areas (see, for example, Turkeltaub et al., 2012), but most studies so far have focused on language areas such as Broca's and Wernicke's areas, which are core regions in language production and reading abilities, among others (e.g., Cattaneo, Pisoni, & Papagno, 2011).

Attention Deficit Hyperactivity Disorder (ADHD)

The economic costs of the consequences of ADHD are particularly high, as they involve medical costs, including the treatment of psychiatric and medical comorbidities, as well as high levels of criminality and unemployment (Matza et al., 2005). tES is therefore an attractive potential intervention technique to alleviate some of the behavioral and cognitive problems associated with the disorder. In ADHD, the pattern of atypical brain

development is complex and involves a variety of cortical and subcortical areas. Symptoms of impulsivity and attentional deficits are accompanied by delayed cortical maturation in right and, to a lesser degree, left prefrontal cortices (PFCs) (see, for example, Shaw et al., 2012). Underdevelopment of the right PFC is thought to cause ADHD-related deficits in response inhibition, whereas the DLPFC is responsible for the observed reductions in, for instance, divided attention, both of which are impaired in ADHD (e.g., Pasini, Paloscia, Alessandrelli, Porfirio, & Curatolo, 2007).

Krain and Castellanos (2006) discussed a range of available evidence, but also inconsistencies, for globally reduced brain volume, including gray (and white) matter reductions in the basal ganglia, the frontal cortex, and the cerebellum. Non-invasive stimulation of deep brain structures, such as the basal ganglia, is challenging at the moment, as there is no fixed protocol to reach such structures effectively. The effects of tES on the cerebellum are currently less clearly understood than on neocortical areas, but have already been shown to affect cognition, motor performance, and procedural learning (for a discussion, see Ferrucci & Priori, 2014) and may therefore improve ADHD deficits. In contrast, prefrontal areas are easily accessible with tES, and a wider range of experimental evidence regarding its effects on higher-level cognition is available that is relevant to ADHD intervention (see, for instance, Ditye et al., 2012; Hsu et al., 2011; Weiss & Lavidor, 2012). As demonstrated through magnetic resonance spectroscopy (MRS) measures of cortical glutamate and GABA, individuals with ADHD also show regional abnormalities in their levels of cortical excitation and inhibition, which have been related to their behavioral and cognitive symptoms (Arcos-Burgos et al., 2012; Carrey, MacMaster, Gaudet, & Schmidt, 2007; Edden, Crocetti, Zhu, Gilbert, & Mostofsky, 2012). It is therefore most practical to attempt to reduce the behavioral and cognitive disinhibition by modulating prefrontal and motor cortex excitability (Ditye et al., 2012; Jacobson, Ezra, Berger, & Lavidor, 2012). With the advancement of non-invasive brain stimulation techniques, we will hopefully be able to directly affect deeper brain structures in the future (see Chapter 19).

THE YOUNG AND PLASTIC BRAIN

Given the current uncertainty about the effects of tES on the developing brain, one might wonder why we should not wait until the child has reached an age at which stimulation is predictable and safe. Aside from the cumulative negative effect that learning disabilities have on the child's life, the other main reason for such intervention is the increased potential for plastic changes during child development. Animal research has shown that silent synapses in certain circuits of the developing rat brain can be

made functional by the induction of LTP (Feldman, Nicoll, & Malenka, 1999). Furthermore, certain mechanisms of receptor functioning promote the interaction between LTP and LTD and thereby regulate experience-dependent changes in the circuits. However, these mechanisms decrease after the end of the sensitive period (Crair & Malenka, 1995). The effects of plasticity may therefore originate from the activation of silent synapses, the efficiency of which is subsequently regulated by LTP and LTD, causing plastic experience-dependent changes (Feldman et al., 1999). With development and maturation the cortical layer becomes thinner, such that cortical connections are relatively stable and less prone to flexible changes (Gogtay et al., 2004; Knudsen, 2004).

During a sensitive period, glutamatergic activity is crucial for the induction of cortical plasticity and reorganization (Schlaggar, Fox, & O'Leary, 1993). tES is therefore likely to support neural activity in networks that show deficient excitability. Such sensitive periods are also marked by an enhanced excitation/inhibition (E/I) balance, which can be modulated artificially even outside these periods. This can be achieved using a variety of different means, including neuromodulatory medication or certain kinds of training and enrichment, that can modify the E/I balance to allow higher levels of plasticity (Bavelier, Levi, Li, Dan, & Hensch, 2010). tES, as the current evidence demonstrates, has the potential to modulate this E/I balance during a later period, where there is normally a relatively high degree of stability in cortical synapses. This may be beneficial in adults, who have reached a relatively stable synaptic system, but also in children with atypical development, who have more stable or limited capacity for plasticity in critical brain regions (see Figs 16.1, 16.3). It is also important to note that such a trajectory in brain organization is linked to different domains of cognition that peak at different stages of child development in terms of the opening and closing times of their sensitive period (see Bardin 2012; McCain, Mustard, & McCuaig, 2011).

A DREAM COME TRUE: tES IN THE CLASSROOM?

At the moment, applying tES in the real classroom is an idea that requires further development. It might be more cumbersome to use it in groups where electrodes need to be fitted on each subject, and from the ethical point of view it might also cause discomfort or anxiety, especially in the case of children. New developments, such as wireless electrical stimulators (e.g. Starstim Neuroelectrics® stimulator (Barcelona, Spain) would make it possible to apply non-invasive electrical brain stimulation in the real-life classroom setting, where it is most relevant for real-life application. Compared to highly-controlled research settings, where participants mostly perform computer or paper-and-pencil tasks, wireless

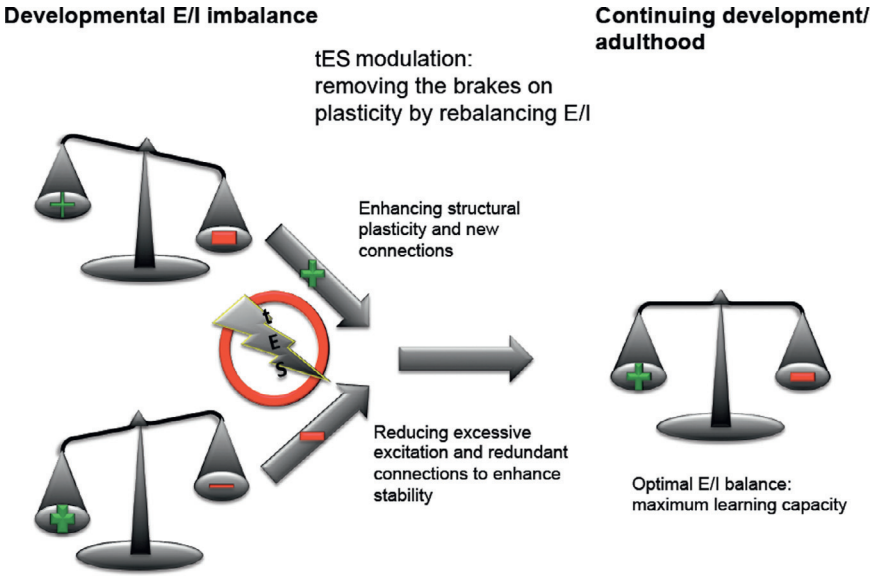

FIGURE 16.3 tES is aimed to increase inhibition or reduce excitation during atypical brain development. Targeted tES thereby modulates the E/I balance and removes the brakes on learning and normal brain development, so that the rebalanced E/I system allows for maximal learning and consolidation throughout further development. The eventual brain dynamics can become more efficient due to tES intervention (see also Bavelier et al., 2010).

tES can be applied while children learn through educational instructions and explanations. A possibility is to even use the stimulation in a group of children, which may provide a more supportive environment under close attention of expert educators.

Using a wireless stimulator, the individual wears a head cap similar to a rugby cap (which can also be tailored to fit the child's personal taste) onto which the electrodes are mounted. The receiver can therefore move around freely in space and is not restrained by the wires. For example, this allows a child in the classroom to use the blackboard in front of the class. In addition, the cap ascertains that the electrodes are held in place and will not slip or lose connection to the scalp. It is more useful to apply the stimulation in an environment where the learning occurs directly, in order to enhance the ability to integrate new information. Depending on the desired outcome, simultaneous tES and training can be individually adapted by the administrator, and can be flexibly adjusted in terms of the content and the complexity of the task material. Depending on the desired outcome, the administrator can therefore determine whether to target global or more specialized cognitive functions. This type of intervention also minimizes the number of staff necessary for successful training, and the time needed to achieve the desired outcome. Depending on

the type and intensity of the stimulation, the child might not even notice when the stimulation starts and therefore should not be affected by any discomfort (Looi and colleagues, personal communication). Overall, optimizing the use of tES by combining it with appropriate learning material offers the possibility for more effective learning, especially for those with learning difficulties.

POTENTIAL RISKS AND ETHICAL CONSIDERATIONS

The research using tES in child populations is currently extremely limited, and therefore definitive predictions about the tolerability of tES cannot be made until the field gains more experience (Kessler et al., 2013; Looi & Cohen Kadosh, personal communication). It is important to consider that, due to the smaller head size, the same dosage of tES is likely to have a more intensive effect on a child's brain than on an adult brain (Minhas, Bikson, Woods, Rosen, & Kessler, 2012). Some early studies, however, have indicated that young children from the age of 5 years onwards tolerate the stimulation well, even at higher intensities of 2 mA. Only minor side effects have been observed, such as tingling, itching, and mood changes (Andrade et al., 2013; Mattai et al., 2011; Schneider & Hopp, 2011). The current is typically ramped up and ramped down at the end of the stimulation period in order to increase tolerability or to avoid irritation, whereby the skin can gradually accommodate the change in current flow (Guleyupoglu et al., 2013).

In addition to concerns about tolerability, there is also a risk of cumulative effects of the stimulation – for example, daily administration of tDCS leads to higher cortical excitability than when the stimulation is applied every other day (Alonzo, Brassil, Taylor, Martin, & Loo, 2012). The duration of aftereffects is crucial for the purpose of rehabilitation and treatment, and the duration of the stimulation itself, as well as intersession intervals, affects the duration of such aftereffects (Monte-Silva, Kuo, Liebetanz, Paulus, & Nitsche, 2010). Individuals with a personal or family history of seizures should generally be excluded from tES studies or treatments. This is important because the enhancement in cortical excitability may increase the risk of seizures. It should be noted, however, that seizure thresholds could be experimentally down-modulated in epileptic children using C-tDCS (for a brief discussion, see Vicario & Nitsche, 2013b). In addition, patients with skull traumas or metal fragments stuck in their head area are at risk of side effects, due to the unpredictability of current flow. Similarly, neuro-active drugs might act on cortical excitability. In our opinion, for the current purpose of cognitive enhancement, individuals using any kind of medication should be excluded to avoid potential interactions with the stimulation, and in order to prevent

cumulative effects of the stimulation (see Chapter 6). Moreover, it should be ascertained that if individuals have participated in any other brain stimulation research or treatment, the wash-out period is sufficiently long (Davis et al., 2013).

As Pascual-Leone and colleagues stated, "A system capable of such flexible reorganization harbors the risk of unwanted change" (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). They warned of the consequences caused by practice or restraint, as well as by non-invasive brain stimulation to enhance neuroplasticity. Their warning is especially relevant during developmental periods of high levels of plasticity, as the effect and consequences of shaping a wrong pathway of synaptic connections can be difficult or impossible to reverse (Knudsen, 2004). Cognitive tES training effects in adults have been observed up to 6 months later (Cohen Kadosh et al., 2010; Snowball et al., 2013), which is highly advantageous for positive changes in behavior and cognition, but deleterious if the outcome is negative. As the long-term effects of tES are currently unclear in child populations, future studies should include follow-up assessments to monitor the longevity of tES-induced effects, and other potential side effects. It is important that researchers consider the potential consequences and adapt their research techniques to modulate brain plasticity efficiently and safely, with limited or no physical or psychological side effects.

When considering neural changes induced by tES, it is not only the intra-regional balance between excitation and inhibition that plays an important role in the behavioral outcome, but also interhemispheric and inter-regional connections, and interactions of excitation and inhibition (Pascual-Leone et al., 2005). For example, in a tDCS study in which subjects received stimulation either to their DLPFCs or their posterior parietal cortices, it was demonstrated that, for each region, certain aspects of numerical learning and competence were enhanced while others were compromised (Iuculano & Cohen Kadosh, 2013). This illustrates how unpredictable changes in plasticity can be. One region may become functionally stronger but consequently exhibit inhibitory effects on other regions, or might require more resources, compromising other brain regions, which is observable in behavioral deterioration (Brem, Fried, Horvath, Robertson, & Pascual-Leone, 2014; Pascual-Leone et al., 2012; see also Chapter 19). These consequences that could affect targeted and/or untargeted behavior must be avoided and careful monitoring carried out during periods of treatment, such that it can be terminated if necessary. In this respect, it is of great importance to prevent parents or adults from purchasing their own stimulators and trying out their own intervention ideas at home (for a more detailed discussion on the risks, see Cohen Kadosh, Levy, O'Shea, Shea, & Savulescu, 2012, and Chapter 3).

Similar to the issue of inter-regional effects of tES is the interpretation of the initial neural impairment. While some atypical patterns of brain functioning (in both function and structure) are indicative of the original cognitive impairments, mechanisms compensating for these symptoms may be present (see, for example, Fassbender & Schweitzer, 2006). These in turn are also associated with specific atypical patterns in the brain and can easily be mistaken for a to-be-stimulated brain area. Careful interpretation of the brain-deficit and brain-compensatory mechanisms for the specific cognitive deficit is therefore necessary to avoid the induction of maladaptive plasticity.

It is also important to note that brain areas mature at different speeds, and their peaks for plasticity occur at different time points during development (see Fig. 16.1). The cortex develops in a back-to-front fashion, in which simpler sensory areas mature first, followed by more complex processing and, eventually, higher cognitive abilities associated with prefrontal areas (Gogtay et al., 2004).

In terms of the safety and comfort of using tES, it is crucial to consider risks such as the induction of seizures, unwanted long-term cognitive changes, irritation or damage of the tissue, or feelings of discomfort during stimulation. The potential benefits in many cases might outweigh the low probability of these risks if safety guidelines are followed carefully (see also Chapter 18). Considering that the small cost of discomfort during stimulation (e.g., tingling or itching) might be returned with better future prospects, we suggest that tES should be tested as an intervention method in child populations with learning disabilities and behavioral disorders.

CONCLUSION

tES is a relatively new and promising tool that has the potential to reduce learning and behavioral deficits in adults, and to ameliorate developmental disorders. The adult experimental literature has grown large enough to provide promising results for a large variety of cognitive functions and behavioral improvements (see Chapters 12–15). With further refinements and more targeted application to child populations, tES is likely to redirect some of the developmental brain deficits during childhood and thereby benefit the child on a long-term basis. Similar to every novel method, tES-induced effects in such populations need to be established and carefully monitored in order to prevent accidental reductions in performance (Krause et al., 2013). For safety reasons, over-motivated parents should be educated on the infancy of this method and its potential negative consequences, to avoid misuse. We think that with adequate and careful safety considerations, tES is a promising method to modulate

deficits in neural processing and therefore improve learning and behavioral deficits in both children and adults.

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