Chapter 8
The Human Experiment: How We Won't Win the Rat Race. What Can We Learn from Brain Stimulation in Humans and Rats About Enhancing the Functional Neurobiology of Higher Cognitive Functions?

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Abstract This chapter addresses neuroenhancement and is divided into three parts. Firstly, neuroenhancement is considered in terms of the current societal context of a growing reliance on high level cognitive functions for economic competition. Then, specific research examples involving an increasingly popular neuroenhancement method, transcranial direct current brain stimulation, are discussed regarding what contributions enhancement technologies can make to these higher level cognitive functions. Speculations are made about the dynamics of relationships between brain structures and functions. The complexity of the involved brain mechanisms is discussed to highlight the intricacy of neural engagement to support these functions. And finally, the indications from empirical research are re-applied to the current state of the systems that employ higher level cognitive functions. Questions are presented about the viability of the so-called "More is Better" (MiB) model, in relation to neuroenhancement and for supporting cognitive functions.

Keywords Neuroenhancement • Executive function • Optimization • Inverted-U dose-response curve • State-dependence • Task load

Abbreviations

MiB	"More is Better" (model)
BOLD	Blood Oxygenation Level Dependent
NE	neuroenhancement

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ADHD	Attention Deficit Hyper Activity Disorder
tDCS	Transcranial direct current stimulation
EF	Executive functions
PFC	prefrontal cortex
TOL	Tower of London test
DLPFC	dorsolateral prefrontal cortex
RT	reaction times
ACC	accuracy
rTMS	transcranial magnetic stimulation
PET	positron-emission tomography
DA	dopamine
PISA	Programme for International Student Assessment

8.1 Introduction

In the context of a growing global competition for resources (EEA 2010), there is a common perception that growth will support higher rates of employment and resource productivity, in addition to better living standards (Merkel 2007). At the governmental level, greater competition through technological innovations and economic integration is encouraged as a palliative measure to reduce unemployment rates and stimulate economic growth. A drive to overcome a perceived deficit of workforce to fulfill economic needs may contribute to the public and institutional impetus towards working harder or longer, with the aim to produce better conditions. The idea that "more is better" is a model that may have been conceptually popularized during the Industrial Revolution in which large scale production at low cost solved supply and demand. The rise in productivity due to technological sophistication is a laudable human achievement that is associated with an improved quality of life. Also, thanks to technological advances, humans rely increasingly less on physical prowess in their daily work lives and more on their mental faculties, which creates an increasingly sedentary lifestyle (Paffenbarger et al. 1986). A transition from the "industrial society" to the "knowledge-based" society is important for sustainable development (Merkel 1998). As a result, greater reliance upon cognitive functions, such as the ability to monitor and manipulate information, plan, form strategies, solve problems and make decisions has emerged.

Enhancement technologies have been long available and are stimulated by economic competition. Currently a surge in interest in "neuroenhancement" (NE) has been spurred by attention in the media, science and medicine (Farah et al. 2004; Galert et al. 2009; Larriviere et al. 2009). The definition has generally been taken as the use of pharmacological substances to improve neural function, which can include cognition and mood (Greely et al. 2008). The word "enhancement" itself implies an increase of quantity, value or power, though it does not always mean an improvement. A meta-analysis of misuse of stimulants related to Attention Deficit Hyper Activity Disorder (ADHD) among students suggests that neuroenhancement

is an existing issue (Wilens et al. 2008). Despite concern and assertions about the imminent trend for increased substance misuse, empirical data from population sampling revealed that the annual prevalence rates for non-medical use of prescribed pharmacological substances in pupils and students is as low as 4.1–5.4 % in America (Sussman et al. 2006) and 0.3 % in Germany (Franke et al. 2011). Users' tendency to misuse other substances also suggests that addiction disorder may be as relevant as substance misuse for study aids. Furthermore, literature reviews of the efficacy of memantine, anti-dementia drugs, methylphenidate and modafinil on cognitive performance do not provide firm conclusions and indicate weak if negligible effects on cognition (Normann et al. 2010; Repantis et al. 2010a, b).

This evidence suggests that with pharmacological enhancement, more (e.g. substance) is not necessarily better. This could simply be due to poor experimental designs, since studies often included only single-dose trials with testing over a short time period, and without concurrent training or learning. When found, positive effects were often associated with deficient states, such as with sleep deprivation or in disorders such as ADHD (see reviews above). A focus on enhancement itself can eclipse the implied underlying aim, which presumably is optimization of a given function. If a technological enhancement confers improvement, the underlying mechanisms should be evaluated in order to broaden their applicability and ensure safety. Apart from efficacy and prevalence, the safety and ethics are far from being established, which makes this form of "enhancement" seemingly less viable than presumed (Flower et al. 2010; Quednow 2010). Neuroenhancement is not limited to the misuse of pharmacological substances. Other forms of NE include cognitive training (Brenes 2003; Olesen et al. 2004; Klingberg 2010; La Rue 2010), meditation (Chiesa et al. 2011), exercise (Pereira et al. 2007; Lambourne and Tomporowski 2010; Yanagisawa et al. 2010) and brain stimulation (Siebner et al. 2009; Zimerman and Hummel 2010). The following chapter will consider a particular technology used for brain stimulation.

Transcranial direct current stimulation (tDCS) is a method of brain stimulation used in humans and animals to transiently alter neuronal excitability via weak direct currents with the aim to alter functions associated with the underlying cortical areas (Stagg and Nitsche 2011). Depending on the brain region being stimulated and the polarity used, the excitability can be increased or decreased (anodal and cathodal respectively), which generally makes a cell more or less likely to spontaneously fire. The duration of stimulation and current strength also influence the duration and intensity of the after-effects, which can last up to 1 h (Nitsche et al. 2003, 2007). Due to these effects, tDCS shows promise for use in clinical applications to treat neurological (e.g. stroke) and neuropsychiatric (e.g. depression) disorders (Schlaug and Renga 2008; Nitsche et al. 2009; Utz et al. 2010). It is unclear which electrode montage, treatment frequency and current intensity will result in the most optimal effects for any disorder; however, recently for healthy participants, a dose-response curve was reported in regard to learning (identification of concealed objects) in which a higher current intensity lead to greater performance benefits (Clark et al. 2010). Whether the MiB model always applies to tDCS effects on structure-function deserves further attention, though data suggest that the relationship is more complex.

More recently tDCS is being studied in rat models to evaluate the brain effects at the cellular and molecular level, which may elucidate why tDCS results in functional improvements (Liebetanz et al. 2006a, b, 2009b; Takano et al. 2011). The efficacy of prospective treatments developed for humans can be enhanced by animal models, which emulate in-tact and pathological functions to study the underlying neurobiology of higher-order cognitive processes.

8.2 Consideration of Scientific Results

Executive functions (EF), defined as the cognitive capacity to regulate and control behavior, include goal formation, planning, execution of goal-directed plans and effective performance (Jurado and Rosselli 2007). EF is a component of higher cognitive function that is essential for successful daily living and a high quality of life. Human evolution is associated with increased brain size and metabolism (especially in the prefrontal cortex (PFC)), which are concurrent with expanded capabilities in cognitive function (Fu et al. 2011). Executive functions, particularly those depending on working memory and planning ability, degrade with age (Penner et al. 2010). The functions that are generally targeted for neuroenhancement encompass EF, which are associated with the neocortex of the human brain and specifically the PFC (Leh et al. 2010). EF deficits are prevalent in frontal lobe associated disorders such as depression and schizophrenia (Martinez-Aran et al. 2002; Ottowitz et al. 2002) or frontal lesions (Jacobs et al. 2007), emphasizing the integrity of the prefrontal cortex as essential for intact performance. For this reason, in this chapter the prefrontal cortex is used to serve as a model system to consider plasticity-related changes in function.

Though limited in scope, the following research examples address the use of one particular NE technology and its impact on higher cognitive functions. In the following studies, brain stimulation by tDCS was used to manipulate working memory and skill learning, which support EF. Possible underlying mechanisms to explain the results will then be considered. Since successful visuospatial working memory is associated with increased prefrontal activity and supports problem solving and planning (Newman et al. 2003; Olesen et al. 2004), it is reasonable to posit that altered activity in these areas can lead to altered functions. tDCS of the frontal cortex in rats has been found to affect the hemodynamic activity in the frontal cortex and in more distal regions (Takano et al. 2011). In the following studies, tDCS was applied to the PFC in humans and the frontal cortex of rats to test for performance changes on PFC-related tasks of working memory and skill learning.

8.2.1 Human Study

The Tower of London test (TOL) is a neuropsychological test to evaluate executive function (Fig. 8.1) and is sensitive in revealing impairments in patient performance

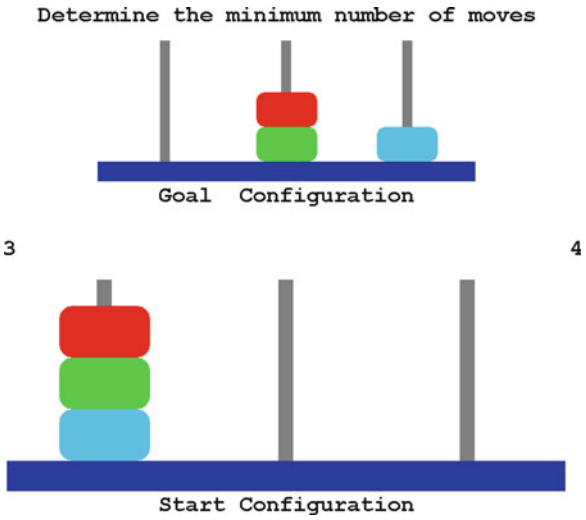

Fig. 8.1 The TOL test is a puzzle involving beads that "slide" on pegs which must be moved to match a designated goal configuration. The "start" and "goal" configurations are presented on the computer screen with two answers at the sides of the screen. In this version, subjects must mentally determine the minimum number of moves necessary to reach the target configuration and press the button corresponding to the side of the screen with the correct answer

relative to healthy subjects (Shallice 1982). Neuroimaging and lesion studies reveal that TOL performance involves a distributed network of integrated brain activity to produce planning, including bilateral dorsolateral prefrontal cortex (DLPFC) activation (Unterrainer and Owen 2006). Planning performance is supported by working memory, and the left DLPFC has been thought to be the critical structure for solving working memory problems with higher task loads (Olesen et al. 2004) and relational complexity (Kroger et al. 2002). In the TOL, graded activation increases have been found in relation to increased task difficulty (a higher number of moves) (Baker et al. 1996; Newman et al. 2003; Unterrainer and Owen 2006). A number of patient populations show deficits in TOL performance including those with frontal lobe damage (Shallice and Burgess 1991), schizophrenia (Tyson et al. 2004; Rasser et al. 2005; Ungvari et al. 2008), depression (Elliott et al. 1997; Goethals et al. 2005), dementia (Rainville et al. 2002), and Parkinson's Disease (Beauchamp et al. 2008; Rektorova et al. 2008). Patient performance, particularly at higher levels of task load, is distinguishable from healthy controls, and neuroimaging studies support the DLPFC as the most critical structure for solving the TOL task (Owen et al. 1990; Grafman et al. 1992; Owen 1997; Rainville et al. 2002; Lazeron et al. 2004; Rasser et al. 2005; van den Heuvel et al. 2005). Cognitive skill learning depends on the prefrontal cortex; it is the ability to acquire how to solve complex problems in intellectual tasks through practice, which, in turn, improves performance (Cerella et al. 2006). Repetition of the TOL test also leads to cognitive skill learning (Ouellet et al. 2004).

To determine the efficacy of brain stimulation-induced activity changes, a study in healthy students was designed to investigate the effects of tDCS over the left DLPFC on planning performance in the TOL test over multiple sessions (Dockery et al. 2009). Due to the known task-related Blood Oxygenation Level Dependent (BOLD) activation increases (Unterrainer and Owen 2006), it was proposed that anodal tDCS (known to increase excitability and BOLD) would lead to improved

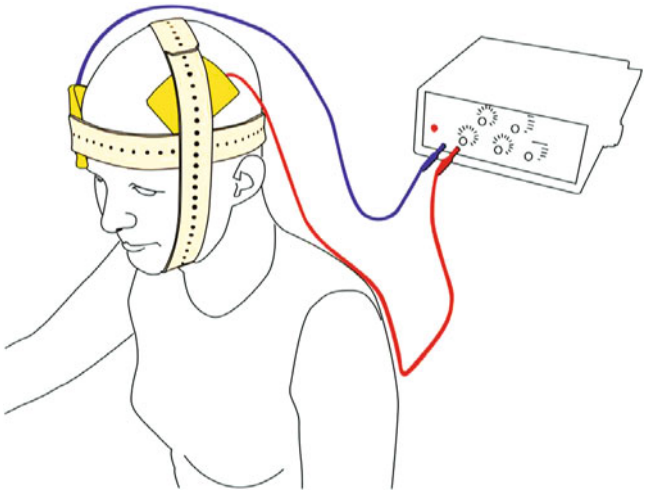

Fig. 8.2 Transcranial direct current stimulation of the left DLPFC and the contralateral right orbit of a human participant. The electrodes, enveloped in wet sponges, are fixed to the head with adjustable latex bands. The stimulator is located out of view of the participant

performance, particularly at high task load levels, while cathodal (known to decrease excitability and often associated with negligible performance effects) and sham tDCS would not. This hypothesis, based on existing literature, was in support of the MiB model. In a cross-over design, 24 healthy participants (5 men, 19 women) performed the TOL test during and after 15 min of active anodal, cathodal and sham tDCS of the DLPFC over three sessions with a long-term follow-up session (after 6 months or 1 year). The 1 mA current was delivered between a pair of water-soaked sponge electrodes (35 cm^2) with electrodes fixed over F3 (International 10–20 system of electrode placement) and contralaterally above the right orbit (Fig. 8.2).

Brain stimulation by tDCS boosted TOL performance for both anodal and cathodal stimulation, causing a significant improvement in planning performance compared to sham tDCS. Anodal tDCS resulted in improvements, particularly in later sessions as indexed by faster reaction times (RT) with equal to higher accuracy (ACC), while cathodal tDCS showed benefits in early sessions leading to a flattened learning curve across sessions due to better initial performance. Retrospectively, the participants were grouped according to the order in which they received the different types of tDCS as defined by: A/C = Anodal before Cathodal, C/A = Cathodal before Anodal. These results were indicated by significant order effects of the stimulation (RT: [$F(1,22) = 8.935$, $p = 0.007$]; borderline for ACC: [F(1,22) 3.494, $P = 0.075$]). In Fig. 8.3 the order effects relating to tDCS sequence are apparent across sessions. A significant interaction for stimulation order and task load (high, low) (RT only: [$F(1,22) = 7.749$, $P = 0.011$]) showed a distinct advantage for tDCS C/A at high task loads (Fig. 8.4). The behavioral results reflect phase-specific performance gains particularly at higher levels of task demand by

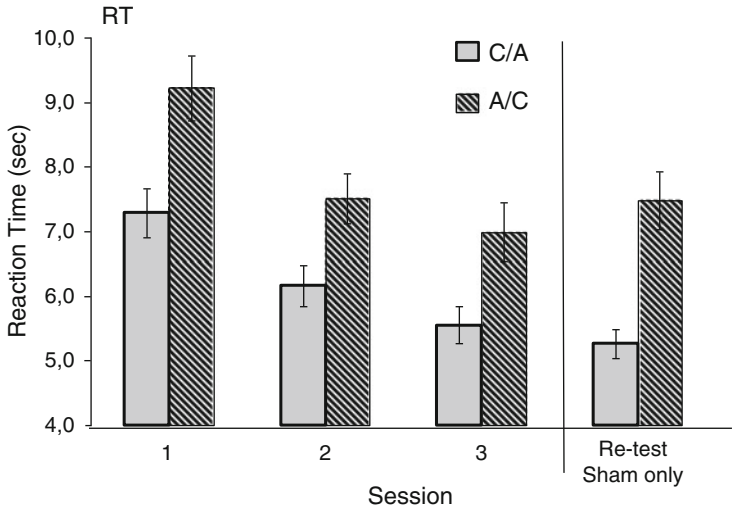

Fig. 8.3 The mean reaction times (seconds) for the TOL task for each order of tDCS sequence (A/C: Anodal before Cathodal, C/A: Cathodal before Anodal) across all four sessions. The order of stimulation conditions was counterbalanced across participants. Error bars indicate ± SEM (standard error of the mean)

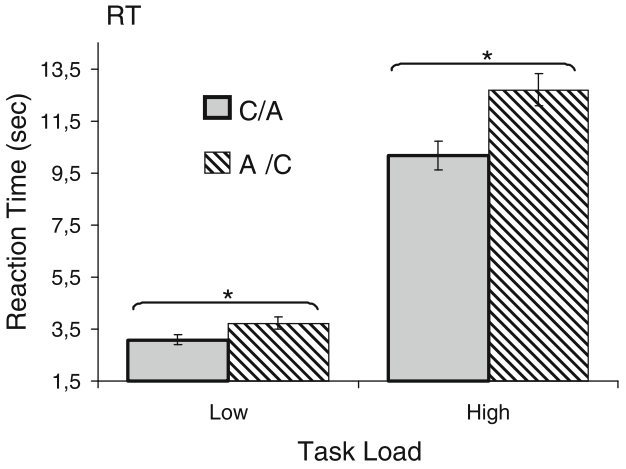

Fig. 8.4 The mean reaction times (seconds) for the TOL task for each order of tDCS sequence (A/C: Anodal before Cathodal, C/A: Cathodal before Anodal) according to task load levels (Low: 1–2-, High: 4–5-move problems). Error bars indicate ± SEM (standard error of the mean)

acute brain stimulation. The results from the re-test session (n = 19) under sham stimulation (at 6 months or 1 year) show that these phase and polarity-specific benefits persist well beyond the acute application (RT only: [$F(1,16) = 17.357$,

P = 0.001]) by which the pretreatment with tDCS C/A during training, yielded a 42 % faster RT than tDCS A/C at follow-up. The long-term cognitive benefits may result as a function of learning mechanisms paired with tDCS-altered brain activity.

8.2.2 Rat Study

Experiments employing animal models combined with tDCS to study its efficacy on cognitive function are rare, if non-existent. This approach would allow for the study of mechanisms of action due to tDCS-induced activity changes and their relevance in regard to learning and memory processes. As it is difficult to study the mechanisms underlying tDCS effects on neural plasticity with humans alone, animal models are needed for bidirectional translational research. To evaluate the potential benefits of tDCS on prefrontal-hippocampal dependent tasks, a novel paradigm for assessing emulated human cognitive functions in a rodent model was developed (Dockery and Wesierska 2010), as was the methodology for transcranial direct current stimulation in rats (Dockery et al. 2011). This may help to increase knowledge about the mode of action of beneficial tDCS effects on cognitive tasks by establishing an animal model that bridges the human studies and supports testing of the neurobiological basis of induced changes. Due to the findings in the previously reported human study, it was proposed that during early learning, cathodal tDCS, known to decrease excitability, would lead to improved performance particularly at high task load levels, while anodal and sham tDCS would not. This hypothesis was not in support of the MiB model, such that more excitability is not necessarily better and the direction of excitability change depends rather on the basal brain activity in order to produce performance benefits.

In the study discussed below involving a rat model, we set out to examine the efficacy of tDCS over the frontal cortex of rats on visuospatial working memory, long-term memory and skill learning in an allothetic place avoidance alternation task (APAAT), in which rats must actively avoid a place where shock is presented (Dockery and Wesierska 2010). Related active allothetic place avoidance paradigms (Fig. 8.5) have shown the task to be hippocampal dependent (Cimadevilla et al. 2001) and the APAAT is associated with prefrontal activity due to its demand on working memory. The APAAT consists of four 5 min conditions: habituation (no shock), two place avoidance training intervals with shock and, after a 5 min delay, a retrieval test (shock inactivated). Over three consecutive days (D1, 2, 3), prior to behavioral training, freely behaving rats received 30 min of 200 μA of tDCS over the frontal cortex (Fig. 8.6), which is thought to increase (Anodal n = 15) or decrease (Cathodal n = 13) neuronal excitability (Liebetanz et al. 2009a) relative to control rats (n = 12). For each training day, the location of the shock sector was alternated. The long term effect of stimulation and training on behavior was tested without tDCS on D21.

Performance improved with place avoidance training, within daily sessions as indexed by a decreased number of entrances ($F_{6,228} = 4.17$; $P = 0.0004$) (Fig. 8.7).

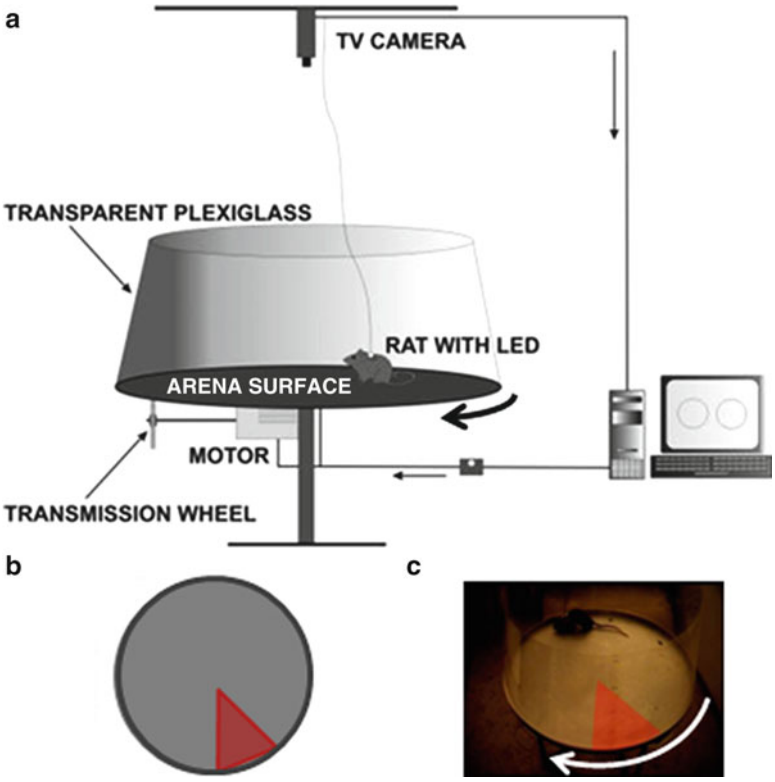

Fig. 8.5 A figure modified from Bubenikova-Valesova et al. (2008) shows a schematic representation of the place avoidance set-up. In (**a**), the arena is depicted located in a room in which salient room-based cues are presented. Via a diode on the periphery of the arena and another on the rat's back, the rat's trajectory can be recorded and monitored by a camera mounted on the ceiling. Thereby coordinates in a 2-D frame, both according to the arena and the room frames can be registered by a computer program (Track Analysis, Bio-signal Group, Brooklyn, New York) and a monitor located in another room. In (**b**), a schema depicts the aerial view of the to-be-avoided sector (e.g. 45° sector) and in (**c**), a photo depicting the scale of the rat on the 80 cm diameter arena relative to the to-be-avoided sector. The *arrows*, depicted in segments (**a**) and (**c**), represent the movement of the arena when the active place avoidance task is being employed

The complexity of the task was ensured by a continuously altered shock sector location each day and was supported by the results, which show that they avoided better on D2 than on D1 and D3 (ENTR: $F\ 2{,}76 = 5.41$; $P < 0.006$; $D1 > D2 < D3$, $P < 0.004$). These results likely express poor performance in the naïve state (D1) and higher load on D3 from exposure to previous shock sectors on D1 and D2. Here, D2 represents the optimum for having advantages from task experience and still a moderate task load. Improved performance was also found within sessions in which skill learning (not depicted) occurred as shown by a low number of shocks per entrance during the second training interval ($F\ 3{,}114 = 39.39$; $P < 1 \times 10^{-16}$;

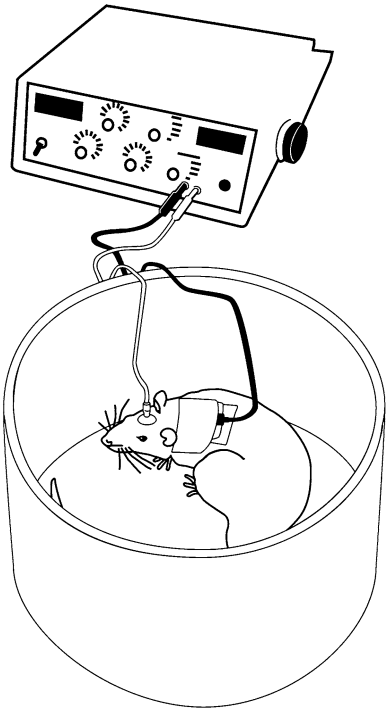

Fig. 8.6 Experimental set-up with transcranial direct current stimulation (figure from the supplementary material in Dockery et al. 2011). The epicranial electrode (target) was plugged into the cannula fixed over the frontal cortex, and the second electrode was strapped to the rat's back by a latex jacket. The constant current was supplied by a portable stimulator (model: CX 6650, Rolf Schneider Electronics, Gleichen, Germany)

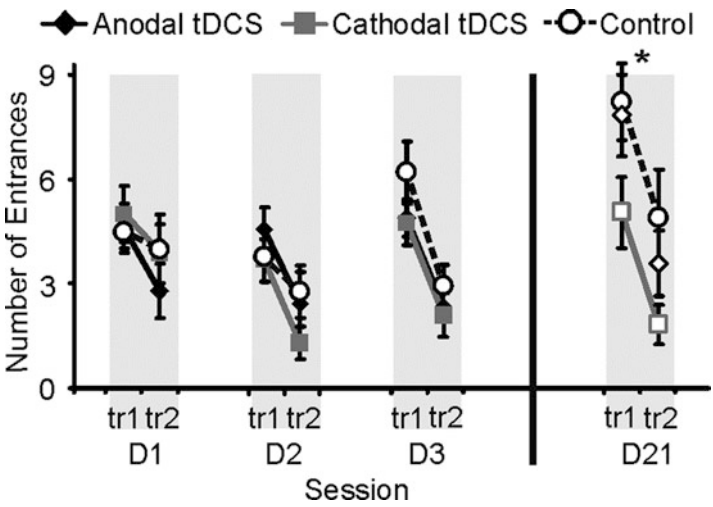

Fig. 8.7 Working memory (partial data from the supplementary material in Dockery et al. 2011). Working memory in the place avoidance task is presented as the number of entrances (ENTR) in reference to the sector to-be-avoided. Values are presented as grand averages ± SEM according to group, day and training condition. The post hoc results, marked by *asterisks*, were equivalent to: ***$P < 0.001$. The *grey bars* indicate an active shock sector. On day 21 (D21) the *unfilled symbols* indicate that tDCS was not administered

ha > t1 > t2 < ts = t1; $P < 0.01$). This means that even though rats must newly acquire the location of the shock sector for each day, their ability to avoid the sector (and not just escape), once they know where it is, improved with training for each session. This ability is referred to as cognitive skill learning.

There is an effect of day on skill learning in which performance is optimal on D2 ($F_{2,76} = 7.50$; $P < 0.001$; D1 > D2 < D3; $P < 0.002$). The long-term benefits of brain stimulation by tDCS on early learning were found on D21 (no tDCS) in rats after cathodal stimulation; the results indicate that these rats performed better with less entrances ($F_{2,37} = 3.61$; $P < 0.036$; $tDCS_a = tDCS_c <$ Contr, $P < 0.07$) and fewer shocks per entrances ($F_{2,38} = 4.67$; $P < 0.015$; $tDCS_a = tDCS_c$, $tDCS_c <$ Contr, $P < 0.02$) during the training intervals than control rats. This suggests that by pairing a highly cognitively demanding task with cathodal frontal tDCS (thought to decrease cortical excitability) during training/early acquisition, later performance (without stimulation) will show advantages. The appearance of latent effects even while no significant differences were found during the training is unusual. It is intriguing in light of the course of long-term plasticity changes with learning and, conversely, with regard to the delayed effects of insult manifesting in neurodegenerative disorders.

Our results indicate that complex cognitive functions, which are frequently associated with pathology in various human diseases and disorders, are captured in our rodent paradigm and that these functions can be altered by tDCS with long-term benefits to performance. This supports the plausibility of neuroenhancement in healthy humans and rats. The cumulative effects of tDCS on visuospatial working memory and skill learning in rats suggest that, as in humans, they are phase-dependent (requiring time and experience) and polarity-specific. Further, since cathodal tDCS conferred benefits, especially under highly novel and highly demanding conditions, there may be a role for exogenously decreased frontal excitability, which may temper the high arousal associated with the task novelty, high load, brain stimulation itself or foot shock. Perhaps the nootropic potential of tDCS of the frontal cortex on spatial memory and learning operates via a kind of anxiolytic effect of inhibitory stimulation on the PFC activity. Based on current literature, this would be particularly advantageous during early acquisition/novelty and under high task demand (Salehi et al. 2010).

8.3 Discussion and Summary

Two major findings emerge from the results: (1) the phase of learning/memory and (2) the level of task load (at least in humans) are important determinants of the efficacy of tDCS effects on frontal cortex function. These findings indicate that the parameters of tDCS (current strength, duration of stimulation, polarity) alone do not determine how the current will alter function due to neuronal excitability changes in the (pre)frontal cortex in healthy young adults and rats. The results also suggest that the existing state of the dynamic system that is targeted must be determined in order

to establish which direction of tDCS-induced changes constitutes an enhancement leading to optimization. Otherwise, the risk in driving the system in the wrong direction is plausible, which is likely due to homeostatic mechanisms. Here, the phase of learning was determined across sessions for humans (same test, 1 week inter-trial interval) and also within sessions for rats (novel task condition each day, 1 day inter-trial interval). In human planning performance, the phase- and polarity-dependent effects were most apparent for the more difficult problems.

The idea that the existing activity state of the PFC (novelty/stress vs. learned state; high arousal vs. low arousal) determines which direction of activity changes affect performance benefits, is in contrast to commonly held ideas that tDCS-induced excitability increase would statically lead to performance benefits, while decreases would lead to null or negative effects. These assumptions are based on the MiB model, that is, that more excitability would result in higher performance gains when the stimulated area is needed for the given task. The results reported here suggest that the MiB model does not always apply, at least not to brain stimulation of the (pre)frontal cortex and function in novel PFC-related tasks.

In rats, phases of learning and memory for a spatial learning task (i.e., acquisition, delay, and retrieval) have been associated with changes in the amount of extracellular dopamine in the mPFC (Phillips et al. 2004). The PFC may differentially modulate distinct phases of visuospatial learning (Rinaldi et al. 2007). The DLPFC is the most crucial site for dopaminergic effects on cognitive functions (Braver and Cohen 2000; Cools et al. 2002) that are associated with endogenous DA release (Aalto et al. 2005; Phillips et al. 2004). This seems appropriate since dopamine (DA) is a neuromodulator implicated in synaptic mechanisms mediating cognitive functions such as attention, learning, memory formation and reward behavior. The plasticity of corticostriatal circuitry and dopamine levels are differentially modulated during different learning phases, with the activity of DA neurons decreased after extensive training compared to the early stages of learning a novel action (Costa 2007). Dopamine release increases during acquisition of novel information (Goto and Grace 2005; Lemon and Manahan-Vaughan 2006), while, conversely, subsequent presentations of a novel stimulus lead to its down regulation in the PFC (Wilkinson et al. 1998).

In humans, working memory capacity increases with training, which yields plasticity of dopamine (D1) receptor densities and brain activity pattern changes (McNab et al. 2009; Klingberg 2010). Concerning the phase-dependent tDCS results, there is much experimental evidence to support the relevance of previous experience of a particular cortical region in constraining the subsequent response to tDCS in a homeostatic manner (Ridding and Ziemann 2010). Our findings stand in contrast to tDCS of the motor cortex, in which increased excitability by anodal tDCS enhances motor performance, while cathodal tDCS reduces improvement in skill acquisition (Vines et al. 2006); in our studies, the behavioral effects of the excitability changes seem to depend on the pre-existing state of the cortex in relation to previous experience and, possibly, arousal. State-dependent effects of tDCS on motor cortex excitability have been shown when pharmacological substances were introduced. For example, anodal tDCS was found to have reverse

effects, inhibiting motor cortex excitability, with L-dopa administration (Kuo et al. 2008). This suggests that more excitability does not necessarily facilitate enhanced plasticity. Furthermore, dose-dependent impairment by a DA D2-like agonist on tDCS-induced motor cortex excitability changes was found, in which "impairment" referred to both blunted plasticity and to a reversal of excitability changes, such as inhibition induced by anodal tDCS at 0.125 mg or excitation by cathodal tDCS at 1.0 mg (Monte-Silva et al. 2009). Besides pharmacological modulation, seemingly paradoxical effects of tDCS on the occipital lobe were found on visual-evoked potentials and attributed to the duration of the polarization and the stimuli used (Accornero et al. 2007). These findings suggest that tDCS stimulation can yield different effects, which are not always enhancements that lead to improved function.

According to the Yerkes-Dodson law, performance improves with increases in arousal level; however, beyond a certain optimal medium point it has deleterious effects (Yerkes and Dodson 1908). This inverted U-shaped relationship exists between task performance and the beneficial effects of dopamine agonists on cognition (Kimberg et al. 2001). Seamans et al. (1998) showed that in rats, working memory depends on the maintenance of an optimal range of DA activity in the medial PFC and that there is phase specificity by selective disruption of behavior with DA receptor blockade. In a PET study, Parkinson's patients, with known DA disturbance, showed altered activity and predominant use of explicit memory strategies to acquire the cognitive skill underlying TOL planning performance at a lower rate of accuracy (Beauchamp et al. 2008). Single-photon emission computed tomography imaging of striatal dopaminergic deficits have been linked to both poor TOL performance and depressive mood (Rektorova et al. 2008). Furthermore, dopamine has been found to modulate task-related fronto-striatal activation and default mode network deactivation in TOL performance (Nagano-Saito et al. 2009).

Not only was learning phase found to be important, but in these studies, task difficulty was also a factor influencing the effects of brain stimulation on cognitive functions. Interestingly, both new situations and harder tasks tend to increase an individual's arousal levels, which relate to activity in the PFC. The level of difficulty of a task influences the connectivity of the brain areas involved in working memory (Rissman et al. 2008). The importance of task load (and associated brain structures) on the MiB model is not trivial, as the inverted U-shape function is thought to be representative for difficult, but not easy tasks since those follow a linear relationship of brain activity and performance (Salehi et al. 2010). This, then, could clearly influence the impact of any stimuli (or brain stimulation) that alter the excitability of the (pre)frontal cortex on cognition. These can include brain stimulation, stressors, mood or prior experience. The impact of these can be greater when task load is higher, as shown by the greater effects of stress on spatial learning and memory in rats when reversal learning was introduced (Salehi et al. 2010).

Apart from learning and memory (Baldi and Bucherelli 2005), there are other factors which modulate an organism's physiology according to an inverted-U shaped dose response curve. This means that both too much and too little are associated with poor performance and in common parlance this is referred to as homeostasis (Chrousos 2009). The body's response to stress can influence the

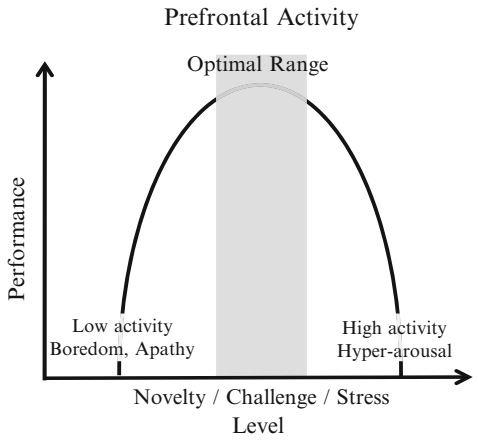

Fig. 8.8 The relationship between prefrontal activity levels and higher level cognitive function follows an 'inverted U-shape' in which only moderate activity results in optimal performance. Data suggest that the likelihood of tDCS of the prefrontal cortex to affect gains or detriments in cognitive performance is related to the existing activity level of the prefrontal cortex, which is known to relate to factors such as novelty, challenge and stress

activity of the prefrontal cortex. The study by Salehi et al. showed that in rats the inverted-U shaped relationship between stress and cognitive functions is most evident during early acquisition as opposed to in over-trained conditions (Salehi et al. 2010). This suggests that the inverted-U shaped relationship is phase-specific. According to Fig. 8.8, it is possible to see how knowing the state of a system, such as prefrontal circuitry, can help determine which changes (direction, amount) can drive it toward more optimal function.

Concerning tDCS effects, to date, no studies have been performed in order to more directly determine extrastriatal DA modulation following acute tDCS of the DLPFC with a specific focus on the prefrontal cortex. Another type of brain stimulation, repetitive transcranial magnetic stimulation (rTMS), showed endogenous dopamine changes (release) in the ipsilateral medial PFC, which were specific to left DLPFC stimulation; these changes were determined by positron-emission tomography (PET) (Cho and Strafella 2009). In the motor cortex, measurement of DA modulation by tDCS using PET has also not been performed. However, DA receptor activation by L-dopa showed nonlinear dosage effects on neuroplasticity for non-focal (Monte-Silva et al. 2010) and focal (Thirugnanasambandam et al. 2011) brain stimulation; the effects indicate the need for an optimal DA level for functional plasticity. Reversed or abolished effects of tDCS effects on excitability were found depending on the L-dopa dosages. This suggests that the MiB model does not apply to the interaction of the dopaminergic system and tDCS effects on neural activity. Experimental data rather support the need for homeostasis of that system. This could be more thoroughly tested in a rat model in which frontal cortex dopamine release could be monitored throughout different learning phases, arousal states and task difficulty levels, and in association with frontal tDCS.

Dopamine has a neuroplasticity-modifying influence on tDCS effects (Kuo et al. 2008), which indicates that while the effects require a physiological concentration of DA, a reversal of effects on excitability can occur depending on the DA level. More is not simply always better. Extremely high or low DA concentrations, for example, due to periods of stress, can alter the DLPFC network balance to incommensurate inhibitory interneuron activation (Kroner et al. 2007). In the PFC, both deficient and exorbitant levels of DA receptor stimulation, expressing an inverted U-shaped function, impair working memory (Cools et al. 2008). Brain stimulation-induced changes in excitability or learning processes themselves can cause inverse or preventative effects on proceeding manipulations of neuronal excitability and synaptic plasticity (Lang et al. 2004; Siebner et al. 2004; Ziemann et al. 2004; Stefan et al. 2006). This model coincides with homeostatic plasticity, whereby low background activity (e.g. pre-treatment with cathodal tDCS in an earlier session) would enhance the associative plasticity related to learning (Nitsche et al. 2007), whereas high excitability (e.g. anodal tDCS) would inhibit it. Likewise, the strength of this homeostatic effect would diminish as learning reached asymptotic levels. This representation of homeostatic plasticity stands in contrast to the MiB model.

In the described human study, for participants who were naïve to tDCS and the TOL test, cathodal tDCS of the DLPFC facilitated acquisition of executive functions as decreased excitability by exogenous stimulation paired with the endogenously increased activation due to a novel task lead to benefits (Dockery et al. 2009). This may be most important during initial learning because less experience allows for a greater number of possible paths to reach the goal and, therefore, a higher likelihood for error. It is possible that cathodal tDCS mediates its early beneficial effect through noise reduction of neuronal activity by metaplastic regulatory dopaminergic activity. Anodal tDCS may confer benefits by exogenously increasing DLPFC activity in the later training phase when basal dopamine (DA) levels have receded, which causes enhanced efficacy of active receptors. An exogenously-induced excitability increase in healthy, naïve participants may not be beneficial during initial exposure to the novel task because a kind of "overstimulation" could lead to excitotoxicity. Though not determined for the PFC in a single session, anodal tDCS of the motor cortex was found in association with decreased GABA while cathodal tDCS was associated with both decreased GABA and glutamate (Stagg et al. 2009).

tDCS provides a tool to induce lasting improvements in cognitive function (e.g. frontal lobe pathologies) and skill acquisition (e.g. learning disabilities) by optimizing neural activity and thereby strengthening the connections associated with compromised prefrontal-hippocampal circuitry or sub-optimal activity levels. The results and theories presented here are not in favor of a general, More is Better approach to brain stimulation of prefrontal-based functions. Translational research aims to elucidate the nature of executive functions by using animal models to investigate generally how they might be enhanced and later apply the findings to humans. With these models it is possible to directly test for an inverted-U-shaped dose response curve between PFC activity changes and dependent cognitive functions. Future work should aim to increase knowledge about the mode of action of beneficial tDCS effects on cognitive tasks by establishing the neurobiological basis of tDCS-induced changes.

8.4 Conclusions

The aim of neural enhancement is to improve cognitive function or mood. To ensure that enhancement equates to improvement, valid tests are needed and must be employed. Otherwise, the efficacy of the NE is unclear, as are the potential safety hazards. With only the research examples given, it is clear that altering brain activity in order to reach performance gains is not trivial or straight-forward. When gains are achieved, the underlying mechanisms are not necessarily easy to estimate or understand. While idealism drives technological advancement, in the case of brain stimulation, it must be moderated by objectivity via empirical evidence from scientific inquiry. Though the studies discussed here did not directly test the physiological basis for the functional changes due to stimulation of the (pre)frontal cortex, they laid the groundwork to directly test such theories. The results reported suggest that the MiB model is not always the most fitting to achieve an optimal performance level, and rather moderate activity is needed to support these high level cognitive functions governed by the PFC. It is clear that rather than make assumptions, direct testing, which requires time and resources, is necessary in order to gain greater understanding.

One method currently engaged with the aim to test the fitness of a society's individuals, is the use of standardized assessment. Such types of assessment aim to measure the capacities of students, in terms of abilities and skills, by a constructed basis of comparison for students of different backgrounds. The Programme for International Student Assessment (PISA), organized by the Organisation for Economic Co-operation and Development, presents PISA test results, which are meant to reflect students' knowledge and capabilities (OECD 2010). The test has been developed to measure the extent to which education systems prepare students for life. This then can help policy makers make informed decisions about how best to "enable citizens to take advantage of a globalised world economy" (OECD 2010). With the PISA results, much speculation has been observable in the media about a country's educational system falling behind, with the implied notion that high scores on standardized tests correlate to students' employability. The notion of MIB is reflected by the Secretary General of the OECD, with the statement, "stay ambitious; work harder to reach your full potential, no matter how you come out in the picture" (Gurría 2010).

If working harder means studying longer and more intensely, the question is whether it helps to enable citizens, in this case, by promoting effective learning and memory in students. Is it necessary to determine the current state of the students in order to determine which conditions will produce the best results? If so, this is an alternative to focusing primarily on the quantity of work load. Furthermore, is it important to verify whether a higher load translates to better learning or better eventual employability? If we empirically know that more work hours or a higher load do not necessarily lead to more desirable results, then what should change about the expectations and also the structures of reward? It is also constructive to determine which institutions are suited to make contributions and assert structural changes to support reform.

Responsibility for development in any evidence-based reform movement does not lie solely on the government or social institutions. Individuals and small collectives also make choices that determine behavioral outcomes. In the research studies addressed here and for other NE methodologies, a question concerning the role of autonomy remains. It is unclear whether NE is even possible without effort. It is plausible that engagement may be a criterion for NE related to improved plasticity in the executive functions, learning and memory. It is interesting that task difficulty plays a role in the relevance of induced changes in PFC-dependent functions since task load influences the connectivity of the brain areas involved (Rissman et al. 2008). Working memory is associated with fluid intelligence through common neural circuitry, and processes related to attentional control, the ability to manipulate abstract relations and maintain possible paths to reach goals (Jaeggi et al. 2008). Previously, it was thought that intelligence was a fixed trait. However, training of working memory, possibly through constant engagement of EF components, has been found to transfer to fluid intelligence (Jaeggi et al. 2008). This training itself requires attention and engagement. If the benefits on working memory are viable only through active engagement of particular functions paired with some form of NE, then NE may simply boost natural mechanisms. This is very relevant considering the importance of brain plasticity for learning and memory. On the other hand, if the mechanisms are in place, why are "healthy" participants not already optimized? If one knows that an optimal state for EF, learning and memory exists, then is it possible to train oneself to recognize and maintain such a state?

Considering the influence of government, institutions and media on work ethic, the question is whether this More is Better model actually results in attainment of goals. Does longer duration and higher intensity in work performance result in better employment rates, more resources and better living standards? Does performance depend on the type of work? This chapter addresses some consequences of applying this model to a complex system such as the structure-function relationship between the prefrontal cortex and executive function. Empirical data suggest that the MiB model is inappropriate for higher level cognitive function. For human evolution it is important to recognize that the MiB model is supported by rhetoric and policy that in the short term drive norms towards skills being upgraded that do not necessarily match the demand, and in the long term lead to an effete labor force. More generally, applying the wrong model to such a homeostatic system as high level cognitive function drives individuals, particularly those most vulnerable, towards possibly irreversible structural damage and pathological function. This then changes the demand for skills. Instead of promoting a model that may not be the best fit to achieve aims of higher cognitive function, government bodies and social institutions can constructively influence economic outcomes through incentives and disincentives that support changes. These reforms would take into account the current state of individuals in society and their workload in order to garner optimal changes.

The popularity of neuroenhancement in the media, science and medicine should not be discounted as it indicates affinity to the concept. Increased attention to the topic is also of concern because it may correlate with a rise in prevalence rates since

people can be influenced by the presentation of reasons to change their behavior despite lack of supporting evidence (Larriviere and Williams 2010). The popularity may indicate a perceived need for the (presumed) advance that neural enhancement may provide. In social systems, due to natural selection, with increased demand on higher cognitive functions, the capacity for such functions would be favored and therefore behavior would be under pressure to follow suit. Both the lay public and the professionals involved in the topic are subject to pressures of increased performance demand. As the renowned developmental psychologist Piaget pointed out, we are unable to recognize the stage of development that we are currently in. While a biological system such as the human brain has natural breaks (e.g. GABAergic system), it seems humans are poor at estimating the impact of when too much is too much, when more in not necessarily better. It appears that despite our evolving (pre)frontal cortex, we are not always making decisions that lead to improvement by employing enhancement.

Despite the enthusiasm for an "enhancement society", as the current Chancellor of Germany once said, "In the long term, 'progress' works against us if it continues to be detrimental to nature" (Merkel 1998). This, of course, applies not only to the earth upon which we live but also to the body and mind that make us who we are.

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