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C.Y. Looi

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List of abbreviations

Abbreviations	Short for	Context
ADHD	Attention-Deficit-Hyperactive Disorder	Learning disabilities
ANS	Approximate Number System	Numerical cognition
BDNF	Blood-Derived Neurotrophic Factor	Protein
BOLD	Blood-Oxygen-Level Dependent	Neuroimaging method
dlPFC(s)	Dorsolateral prefrontal cortex(cortices)	Brain anatomy
EEG	Electroencephalogram	Electrophysiological technique
ENS	Exact Number System	Numerical cognition
fMRI	Functional Magnetic Resonance Imaging	Neuroimaging technique
fNIRS	Functional Near-Infrared Spectroscopy	Neuroimaging technique
GABA	Gamma-AminoButyric Acid	Brain metabolite
LTD	Long-term depression	Neurophysiological process
LTP	Long-term potentiation	Neurophysiological process
MALT	Mathematical Assessment for Learning and Teaching	Cognitive assessment tool
MEG	Magnetoencephalography	Neuroimaging technique
MLD	Mathematical Learning Disabilities	Learning Disabilities
NMDA	N-Methyl-D-Aspartate	Ion channel receptor
PPC(s)	Posterior parietal cortex(cortices)	Brain anatomy
rTMS	Repetitive Transcranial Magnetic	Brain stimulation technique

	Stimulation	
tDCS	Transcranial direct current stimulation	Transcranial electrical stimulation technique
tES	Transcranial electrical stimulation	Brain stimulation technique
TOWRE	Test of Word Reading Efficiency	Cognitive assessment tool
tRNS	Transcranial random noise stimulation	Transcranial electrical stimulation technique
WIAT-II UK	Wechsler Individual Achievement Test, Second UK Edition	Cognitive assessment tool
WM	Working memory	Cognitive ability

Abstract

The ability to learn is critical, whether to survive or to thrive. Research suggests that cognitive training and transcranial electrical stimulation (tES) could modulate neuroplasticity and improve learning and cognition. However, the key challenge of both fields lies in their translational research. In particular, the translational potential of both methods is restricted by the use of training tasks that lacked ecological validity. Using more realistic training tasks, the current thesis explored the effects of cognitive training alone on healthy children, and the combination of cognitive training and tES, compared to training alone in typical (healthy adults and elderly) and atypical populations (children with learning disabilities). Findings demonstrate that cognitive training and tES could improve learning and cognition of typical and atypical populations across different age groups, as modelled using the numerical domain. Specifically, the current thesis highlights the role of content in training outcomes, and the synergistic effects of combining tES and cognitive training on learning, compared to training alone. Furthermore, findings suggest that the combined approach of tES and cognitive training could offer long-term positive outcomes that benefit those with lower baseline cognitive abilities, effects that are meaningful to the real-world, and the possibility of mitigating cognitive trade-offs from training alone. Further optimisation of training design and tES parameters, with the consideration of individual differences and underlying mechanisms are warranted to improve the translational potential of these methods. Given the ethical concerns raised by the use of tES for cognitive enhancement, both scientific research and bioethical discussions are required to guide future directions on improving learning and cognition of the individual and for all.

Introduction

Learning is a fundamental process in life, whether to survive or to thrive. It is the acquisition, modification and maintenance of knowledge and behaviour. The ability of humans to learn is credited to the brain's flexibility to adapt to new situations or changes in the environment, termed 'neuroplasticity' (Berlucchi & Buchtel, 2009). It is thought that neuroplasticity is mediated by the efficiency of synapses, or the strength of connection between neurons, basic units of the brain (Hebb, 1949). Through persistent stimulation of synapses, synaptic efficiency is increased, a mechanism known as long-term potentiation (LTP). Conversely, reduced stimulation of synapses leads to decreased synaptic efficiency or long-term depression (LTD). Such changes in the connections between neurons lead to re-organisation of neural circuits, which result in functional changes that support learning and the adaptation of human brain and behaviour to its surroundings (Bliss & Collingridge, 1993; Lillard & Erisir, 2011; Neves, Cooke, & Bliss, 2008).

While neuroplasticity is a lifelong capacity, the baseline (pre-existing capacity for change) and slope of change in neuroplasticity differ across individuals, across the lifespan and between neurologically 'typical' and 'atypical' populations [for a review, see (Oberman & Pascual-Leone, 2013)]. Neurologically *typical* population include those considered to have average baseline and slope of change in neuroplasticity, reflected by population mean in the range and levels of capacities, and cognitive ability to adapt to environmental needs. Neurologically *atypical* populations are those considered to have baseline and/or degree of plasticity that differs substantially from the population mean, reflected by above or below average range and/or level of capacities, and cognitive ability to change, that significantly affects an individual's life quality and socioeconomic outcomes. Such populations include those with neurological disease(s), disorder(s), learning disabilities, or prodigious skills present at birth or acquired.

Across the lifespan, the degree (levels and scales) of neuroplasticity changes (Lillard & Erisir, 2011; Oberman & Pascual-Leone, 2013). The general view is that the brain shows enhanced capacity for neuroplasticity during early development (Johnston, 2009), sustained neuroplasticity throughout adolescence and adulthood (Valkanova, Eguia, & Ebmeier, 2014), which appears to peak in young adulthood, followed by a gradual but consistent decrease into senescence (S. Jones et al., 2006; S.-C. Li, Brehmer, Shing, Werkle-Bergner, & Lindenberger, 2006). Across individuals, the initial level and degree of neuroplasticity differs depending on individual genetic predisposition (Kanai & Rees, 2011), experiences due to environmental changes (May, 2011), and the interaction between the two. Such variability between and within populations, and across individuals in the baseline and degree of neuroplasticity contributes to differences in the level and rate of learning and performance, and ultimately, cognitive abilities. This is of course, in addition to other factors such as baseline cognitive abilities and non-cognitive factors such as motivation.

Given the impact of cognitive abilities on the individual and society (Beddington, Cooper, Field, Goswami, Huppert, Jenkins, Hannah, et al., 2008), understanding ways to modulate neuroplasticity of individuals with typical and atypical neurological profiles (Clark & Parasuraman, 2014; Cramer et al., 2011; Greely et al., 2008; Sahakian et al., 2015) could improve cognition and quality of life across the lifespan in sickness or in health.

Cognitive enhancement

I refer to cognitive enhancement here as the improvement of human cognition either to restore an impaired cognitive function to previous or average levels, or to raise a cognitive function to a level considered to be 'beyond the norm' (The Royal Society, 2011). Various methods have been used to enhance cognition in typical and atypical populations: pharmacological methods such as psychostimulants (e.g., methylphenidate) and non-pharmacological methods such as education, cognitive training and more recently, brain stimulation [for reviews, see (Brühl & Sahakian, 2016; Clark & Parasuraman, 2014; Dresler, 2013; Looi & Cohen Kadosh, 2014, 2016; Sahakian et al., 2015)]. These methods have been shown to affect different levels of the central nervous system, from molecular, structural to functional to modulate neuroplasticity [for reviews, see (Dresler, 2013; Suo et al., 2016)], with differing effects depending on individual differences (e.g., baseline abilities), situational factors, and the targeted cognitive domain [for reviews, see (Caviola & Faber, 2015; Dresler, 2013; Farah, 2015b)].

Above all, the choice and use of cognitive enhancers is contingent upon its safety and efficacy (Farah, 2015b; Greely et al., 2008). Safety includes the consideration of the mechanisms of action, and potential and risks of immediate, short- and long-term physical and cognitive side effects. Efficacy includes the effectiveness in producing a desired outcome (i.e., type of cognitive effects, extent and longevity of effects) and the costs required (i.e., time, money, effort, physical/cognitive resources, unknown costs), which further leads to the consideration of the method's cost-to-benefit ratio [e.g., (Brem, Fried, Horvath, Robertson, & Pascual-Leone, 2014; Davis, 2014; Maslen, Earp, Cohen Kadosh, & Savulescu, 2014)]. Other considerations include the social and ethical concerns associated with the specific method (Bostrom & Sandberg, 2009; Chatterjee, 2004; Farah, 2015a; Farah et al., 2004; Sahakian & Morein-Zamir, 2011). For example, some have perceived internal enhancements such as pharmacological enhancers as unacceptable over concerns of "unnaturalness" and unfairness (Caviola & Faber, 2015; Faber, Savulescu, & Douglas, 2016) compared to external enhancement such as education, cognitive training and brain stimulation (Cohen Kadosh, Levy, O'Shea, Shea, & Savulescu, 2012).

For the purpose of enhancing learning and performance, it could be assumed that the ideal method(s) would produce specific, yet generalizable benefits or 'transfer effects', which are long-lasting, the goal of learning (Soderstrom & Bjork, 2015). This is of course, apart from fulfilling the basic requirements of being safe, accessible and affordable. Two methods that appear promising based on these ideals are cognitive training and transcranial electrical stimulation. I will discuss the potential and translational challenges of these two methods.

Cognitive training

The term 'cognitive training' refers to the repeated practice on a cognitive task to improve cognitive functions. It is known as a safe, accessible, affordable, and effective method in improving a range of cognitive functions, with no evidence of substantial negative side-effects (Caviola & Faber, 2015). Cognitive training has shown to improve cognitive functions of children (J. Holmes & Gathercole, 2014;

Klingberg et al., 2005; Thorell, Lindqvist, Bergman, Bohlin, & Klingberg, 2009), adults (Au et al., 2014b; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008) and older adults (Ball et al., 2002; Kelly et al., 2014; Lampit, Hallock, & Valenzuela, 2014; Toril, Reales, & Ballesteros, 2014; Willis et al., 2006) with typical and atypical neurological profiles. Training-associated behavioural outcomes were associated with neuroplastic changes at the molecular (McNab et al., 2009), structural (Chapman et al., 2015; Sagi et al., 2012; Takeuchi et al., 2010), resting cerebral blood flow (Chapman et al., 2015; Mozolic, Hayaska, & Laurienti, 2010) and functional (Chapman et al., 2015; Olesen, Westerberg, & Klingberg, 2004; Suo et al., 2016; Takeuchi et al., 2013) levels. The mechanisms of cognitive training are thought to be more confined to the neural substrates that subserve cognitive processes during a specific task, resulting in more specific behavioural changes compared to pharmacological methods and some non-pharmacological effects (e.g., physical exercise). Nonetheless, studies suggest that training gains can be generalised beyond trained tasks (Jaeggi et al., 2008). Such transfer effects have been further categorised as “near”- and “far”- transfer effects (Melby-Lervåg & Hulme, 2013). Near transfers are effects that are observed on domains/tasks that are similar in nature (i.e., content, format), while far transfers are those observed in domains or on tasks that are different in nature.

Typically, weeks of cognitive training has been associated with short- and long-term improvements on training and transfer effects (Au et al., 2014b; Jaeggi, Buschkuehl, Jonides, & Shah, 2011). However, there are mixed findings on training and transfer effects (Melby-Lervåg & Hulme, 2013; Owen et al., 2010; Redick et al., 2013; Shipstead, Redick, & Engle, 2012; van Heugten, Ponds, & Kessels, 2016), which might challenge its relevance and applications to real-life. In particular, there are fewer far-transfer effects than near-transfer effects, and few near-transfer effects are long-term (Melby-Lervåg & Hulme, 2013; van Heugten et al., 2016).

Increasingly, training gains and transfer effects have been found to vary depending on task design (Anguera & Gazzaley, 2015; Jolles & Crone, 2012; Moreau & Conway, 2014; Morrison & Chein, 2011; von Bastian & Oberauer, 2014) and individual differences such as baseline abilities (Jaeggi et al., 2011; Jaeggi, Buschkuehl, Shah, & Jonides, 2014; Zinke et al., 2014), and age (Brehmer, Westerberg, & Bäckman, 2012; Jolles & Crone, 2012; von Bastian & Oberauer, 2014; Zinke et al., 2014) [for other factors such as genetic predisposition, motivation and personality traits, see (Green, Strobach, & Schubert, 2014; Jaeggi et al., 2014; von Bastian & Oberauer, 2014)]. Tasks that are more realistic, engaging (Anguera & Gazzaley, 2015; Moreau & Conway, 2014), adaptive (J. Holmes, Gathercole, & Dunning, 2009), and involves bodily movements (Link, Moeller, Huber, Fischer, & Nuerk, 2013; Moeller et al., 2012) have been associated with more pronounced training effects. Transfer effects are also hypothesised to occur when training and transfer tasks engage overlapping neural systems and/or cognitive resources (Dahlin, Neely, Larsson, Bäckman, & Nyberg, 2008; Reis, Prichard, & Fritsch, 2014; Taatgen, 2013). It appears that optimisation of cognitive training design, with the consideration of individual differences, is needed to promote reliable and stronger training and transfer effects that are long-term, i.e., prolonged changes in behaviour, presumably supported by persistent changes in neuroplasticity.

Transcranial electrical stimulation

Transcranial electrical stimulation (tES) is a form of brain stimulation that is painless, affordable, portable, and relatively safe when used within recommended guidelines (Fertonani, Ferrari, & Miniussi, 2015b; Fregni et al., 2015). It involves the application of weak electrical currents, usually between 1-2mA through electrodes connected to a battery-driven stimulator. TES is thought to facilitate or inhibit cognitive processes by increasing or reducing the local "cortical excitability", which is likely to occur by changing the probability of neuronal population under the stimulation site to be activated or to 'fire' during a task (Nitsche & Paulus, 2000). TES has been shown to enhance cognitive performance and learning within 5 to 6 days of training on a specific task, with long-term effects (Cappelletti et al., 2013; Cohen Kadosh, Soskic, Iuculano, Kanai, & Walsh, 2010; Snowball et al., 2013). The beneficial effects of tES occur only when effort is involved, i.e., during a task, but not on its own (Cappelletti et al., 2013). While tES has its limitations in temporal and spatial resolution (Antal, Nitsche, & Paulus, 2006), it adds value to learning studies by serving as a convenient probe for exploring, and in some cases, enhancing the relevant cognitive functions and performance (Looi & Cohen Kadosh, 2016). In particular, tES could selectively modulate the cortical regions engaged during training to generate behavioural changes specific to the function(s) of stimulated sites (Silvanto, Muggleton, & Walsh, 2008). Such "state-dependent stimulation" is thought to improve the spatial resolution by targeting neuronal populations that are primed by the functions they are involved in (Cohen Kadosh, 2015). This concept was recently supported by experimental data (Hauser et al., 2016). The two most common forms of tES used during cognitive training, and in my own thesis are transcranial direct current stimulation and transcranial random noise stimulation.

Transcranial direct current stimulation (tDCS)

TDCS is the most common form of tES used in studies on cognitive enhancement (Coffman, Clark, & Parasuraman, 2014; M. F. Kuo & Nitsche, 2012; Looi & Cohen Kadosh, 2014). In a typical setup, one "active" electrode is positioned on the scalp above the cortical region of interest following the 10-20 international electroencephalogram (EEG) system of electrode placement, and a "return" electrode is placed elsewhere to close the circuit. It is common for the return electrode to be positioned on the contralateral region of the region of interest, or over the supraorbital (region above the eye sockets), or extracephalic regions (e.g., shoulder). Note that the position of the return electrode could affect the overall current flow pattern through the brain and the consequent modulatory effects (Bikson, Datta, Rahman, & Scaturro, 2010), as behavioural outcomes might be partly contributed by the net result of changes induced by both active and return electrodes in the underlying cortex. Therefore, it is worth clarifying here that both active and return electrodes are exerting an effect (i.e., the return electrode should not be confused its conventional terminology as being a "non-active" electrode). Typically, studies examine the behavioural effects of tDCS by comparing the behavioural outcomes between at least two groups: a real and a sham (placebo) group. The real group would normally receive 1-2mA during a specific task that might last for 20 minutes, while the sham would receive the same current intensity but only for a very short period of time, such as 15 seconds at the beginning and at the end of the task. This brief stimulation allows for experimental blinding, as it is sufficient to induce tingling sensation, mimicking that of a real stimulation, but produce negligible effects at the neuronal level (Fritsch et al., 2010; Gandiga, Hummel, & Cohen, 2006). The success of blinding however, might differ between experienced and naïve participants (Ambrus et al., 2012; Ambrus, Paulus, & Antal, 2010).

Mechanistically, animal and human studies suggest that the effects of tDCS depend on electrical polarity. Anodal tDCS is usually known to facilitate neuronal firing, while cathodal tDCS is commonly known to inhibit neuronal firing of the stimulated cortical region (Bikson et al., 2004; Bindman, Lippold, & Redfearm, 1964; Nitsche & Paulus, 2000). Recent studies however, have reported variability in these 'expected' facilitation and inhibition (Jacobson, Koslowsky, & Lavidor, 2012; Rothwell, 2013), and the attribution of facilitating and inhibiting neuronal firing to anodal and cathodal tDCS respectively, is not as straightforward as assumed (Wiethoff, Hamada, & Rothwell, 2014). The exact mechanisms that underlie the behavioural observations post-tDCS remain unclear. A few mechanisms that might account for these observations have been proposed based on indirect evidence from pharmacological and neuroimaging studies.

Pharmacological studies that used blockers or antagonists to examine the effects of tDCS have suggested the potential involvement of ion channels such as the voltage-dependent sodium channels (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003b), calcium channels and N-methyl-d-aspartate (NMDA) receptors (Nitsche et al., 2003b). Other studies have also linked the effects of tDCS with modulation of neurotransmitter systems such as dopamine (Nitsche et al., 2006) and concentrations of gamma-aminobutyric acid (GABA) (Stagg, Bachtiar, & Johansen-Berg, 2011), glutamate and glutamine (Clark, Coffman, Trumbo, & Gasparovic, 2011) [for a review, see (Dayan, Censor, Buch, Sandrini, & Cohen, 2013)]. There have been reports of changes in oxygen-haemoglobin concentrations of regions close to stimulating electrodes (Merzagora et al., 2010), and perfusions in regions structurally connected with stimulated regions (Stagg et al., 2013). It has been suggested that the excitability/inhibitory balance, indicated by glutamate/GABA concentrations in stimulated areas might mediate the effects of brain stimulation (Krause, Márquez-Ruiz, & Cohen Kadosh, 2013). More recently, tDCS was shown to modulate cortisol levels, suggesting its effects on hormones (Brunoni, Vanderhasselt, et al., 2013; Sarkar, Dowker, & Cohen Kadosh, 2014). Some studies have also proposed that tDCS might improve cognition by directly targeting the intrinsic oscillatory activity, linked with a range of cognitive processes (Hoy et al., 2013). At the network level, tDCS have been associated with significant changes in regional functional brain connectivity (Hunter, Coffman, Trumbo, & Clark, 2013; Keeser et al., 2011; Polania, Paulus, Antal, & Nitsche, 2011a; Stagg et al., 2013).

To date, tDCS has been used on children, adults and the elderly [for review see (Looi & Cohen Kadosh, 2014)], with some studies showing long-term effects up to 6 months post-stimulation (Cohen Kadosh et al., 2010; Reis et al., 2009). Such longevity were thought to be supported by mechanisms similar to those of LTP (Stagg et al., 2011), such as relying on protein (Nitsche, Boggio, Fregni, & Pascual-Leone, 2009), protein synthesis (Gartside, 1968a, 1968b), NMDA receptors known to support LTP (Islam, Aftabuddin, Moriwaki, Hattori, & Hori, 1995; Nitsche et al., 2003a) and LTD, and mediation by polymorphisms in the brain-derived neurotrophic factor (BDNF) gene (Fritsch et al., 2010).

In terms of safety, tDCS has shown to be a relatively safe method for use on humans, with no reports of adverse effects [(Bikson et al., 2016; Fertonani et al., 2015b; Kessler et al., 2013; Poreisz, Boros, Antal, & Paulus, 2007) although, see (Ekici, 2015) for a report of seizure in the treatment of an already vulnerable population]. Tingling is the most common sensation attributed to tDCS. Although, a rare mild burning or pain sensation on the scalp beneath the stimulating electrodes could occur, especially when the level of impedance is high (Dundas, Thickbroom, & Mastaglia, 2007; Fertonani et al., 2015b; Loo et al., 2011). Previous studies have demonstrated that continuous stimulation for 20 minutes (Iyer et al., 2005; Nitsche, Seeber, & Frommann, 2005) and even up to 30 minutes (Boggio et al., 2012; Lindenberg, Nachtigall, Meinzer, Sieg, & Flöel, 2013; Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010) did not raise safety concerns. The maximum electric field in the cortex for the standard primary motor cortex (M1) tDCS montage, which has been used extensively is about 0.4V/m based on most published calculations, which is within the occupational limit (between 0.05 and 0.5V/m) but not the general public exposure limit (between 0.01 and 0.1 V/m), set by the International Commission on Non-Ionizing Radiation Protection (ICNIRP, 2010). It is worth noting that the dosage recommended for general public exposure might be lower than that required to induce desired behavioural outcomes in the laboratory setting (e.g., therapeutic effects, especially within short periods of time); the guideline is aimed at regulating safety of exposure or usage in the workplace under the assumption that individuals would be exposed to such effects regularly and for long periods of time.

Research has shown that tDCS does not alter serum concentrations of human neuron-specific enolase, a sensitive marker of neuronal damage, skin temperature below the stimulating electrodes, or induce brain oedema or changes in the blood-brain barrier and cerebral tissue that are detectable by magnetic imaging (Iyer et al., 2005; Nitsche et al., 2003b; Nitsche et al., 2004; Nitsche & Paulus, 2000). One of the few studies that directly explored the safety threshold of tDCS showed that brain regions on rats occur at a current density of 142.9 A/m^2 for duration beyond 10 minutes (Liebetanz et al., 2009). A linear increase in the size of lesion was found between current densities of 142.9 and 285.7 A/m^2, with a calculated zero lesion size intercept of 52,400 C/m^2. There was no tissue damage when stimulated below this current density or charge density threshold, and there were no signs of risk for accumulative tissue damage after 5 consecutive days of stimulation. It is noteworthy that this threshold estimate is two orders of magnitude higher than that applied on humans, which is between 171-480 C/m^2, indicating that the tDCS dosage used in humans to date is likely to be safe. While this particular study might be of limited practical value to clinical conditions given that it does not provide information about long-term morphological modifications or behavioural changes, it suggest the possibility of optimising future protocols to optimise the effects of tDCS, while reducing or avoiding harm.

Transcranial random noise stimulation (tRNS)

TRNS was first investigated experimentally less than a decade ago. It is the application of alternating currents between -.5 to +.5mA at different frequencies to the scalp, typically between 0.1-640Hz (Terney, Chaieb, Moliadze, Antal, & Paulus, 2008). Unlike tDCS, tRNS operates via an oscillatory current, and it is not dependent on electrical polarity (Terney et al., 2008), allowing it to stimulate brain areas under the electrodes simultaneously [i.e., at the same time, on the same subject (Pirulli, Fertonani, & Miniussi, 2016)]. It has been reported that tRNS allows better blinding for sham conditions, as it has a higher cutaneous perception threshold (Ambrus et al., 2010; Fertonani et al., 2015b). In a perceptual learning study, tRNS was shown to induce stronger behavioural effects than tDCS (Fertonani, Pirulli, & Miniussi, 2011). Given its relatively recent discovery, the mechanisms of tRNS are fairly unexplored, and less known compared to tDCS. The stimulation mode of 'noise' consists of the generation of a random level of current for every 'samples' at the sampling rate of 1280 samples/s (Terney et al., 2008). Current amplitudes that are normally distributed (i.e., with a mean of 0mA) are randomly allocated to these samples. The electrical 'noise' delivered to cortical regions of interest is generated by the random fluctuation of the sample currents between positive and negative amplitudes. TRNS is thought to induce facilitatory effects at both ends of the electrodes (Terney et al., 2008). It was proposed that tRNS enhances neuronal excitability by increasing the activity of sodium ion channels (Fertonani et al., 2011; Terney et al., 2008). Another theory is that tRNS operates via mechanisms of stochastic resonance; it introduces random 'noise' to the neural system, which enhances the detection of weak neural signals (Miniussi, Ruzzoli, & Walsh, 2010; Ward, Doesburg, Kitajo, MacLean, & Roggeveen, 2006). This phenomenon was demonstrated by a recent study, which showed that when an optimal level of noise via tRNS was added to the visual cortex, detection performance improved significantly (van der Groen & Wenderoth, 2016). In line with both theories, the effects of tRNS were attributed to transient modulation in blood oxygenation-level dependent (BOLD) response (Chaieb et al., 2009), potentially indicating less noise in the system (Matsuoka, Abbas, Rubinstein, & Miller, 2000) and/or change in synaptic activity. Another study reported more efficient neurovascular coupling in stimulated regions after tRNS applied during training, consistent with observed behavioural improvements (Snowball et al., 2013). The authors proposed that the amount of endogenous electrical noise might have been reduced, leading to a reduced level of responses in regional cerebral blood flow to maintain neural activity. In the same study, behavioural improvements attributed to tRNS were maintained during a 6-month follow up study. It was suggested that such long-term effects in the absence of further stimulation might have been supported by indirect mechanisms such as structural changes to the cerebrovasculature. This idea is consistent with previous animal studies that found significant angiogenesis and upregulation of angiogenic vascular endothelial growth factor after electrical stimulation (Baba et al., 2009).

While the mechanisms of both tDCS and tRNS remain to be elucidated (Bestmann, de Berker, & Bonaiuto, 2015; Fertonani & Miniussi, 2016), there has been a surge in the interest and use of tES for cognitive enhancement (Fitz & Reiner, 2013). The growth in do-it-yourself (DIY) communities, and companies selling tES devices for personal use is a cause for concern, given challenges of current research and the ethics surrounding the use of tES for cognitive enhancement (Davis, 2014; Riggall et al., 2015).

In particular, the ecological validity of tES findings has been questioned, as most studies are conducted within the laboratory setting that require intensive training on simple tasks with little resemblance to the real-world. While significant behavioural improvements have been reported when compared to sham conditions, the scale of change and the ecological validity of such effects in the natural, messy real-world remains to be demonstrated (Pascual-Leone, Horvath, & Robertson, 2012).

Furthermore, given the inconsistencies in the effects of tES across individuals (Krause & Cohen Kadosh, 2014), it remains unclear how the effects of tES are modulated by individual differences. Understanding the size and extent of effects of tES in the real world, and influences of individual differences is warranted to prevent the waste of resources (time, money and effort) of individuals and society.

Next, although the use of tES for cognitive enhancement has not been linked to any minor or major health concerns [although, see (Ekici, 2015) for a report of seizure in the treatment of an already vulnerable population], moral and social concerns have been raised (Brem et al., 2014; Chatterjee, 2004; Cohen Kadosh et al., 2012; Farah et al., 2004; Hamilton, Messing, & Chatterjee, 2011). For example, would tES increase the function of those with already higher baseline cognitive abilities, and hence further widen the natural gap in cognitive inequalities? Could individuals decide on behalf of vulnerable populations such as children whether or not to use tES for cognitive enhancement? The topic on the use of tES on children in particular, has stimulated important discussions on the ethics of its use on vulnerable populations (Cohen Kadosh et al., 2012; Davis, 2014; Maslen, Earp, et al., 2014). However, there is currently a lack of empirical evidence on this topic to fuel discussion.

Finally, few studies have demonstrated that behavioural improvements attributed to tES might have occurred at the expense of impairment of another, or “cognitive costs” (Cappelletti, Pikkat, Upstill, Speekenbrink, & Walsh, 2015; Iuculano & Cohen Kadosh, 2013; Sarkar et al., 2014). Such reports provoked questions of whether tES is really enhancing cognition, and whether its underlying mechanisms follow the rule of the zero-sum game, whereby every improvement must occur at cost of an impairment elsewhere, given a finite resource system (Brem et al., 2014). If that were the case, would it be acceptable to selectively improve one cognitive function at the cost of impairing another? Clearly, empirical evidence is needed not only to advance our scientific understanding of tES, but also to advance the critical analyses of its impact at the individual and societal levels.

One approach to explore the impact of tES for cognitive enhancement (efficacy, cost-to-benefit ratio, effects on meaningful measures) is by investigating its effects on a cognitive domain that varies between- and within typical and atypical populations, with strong individual and societal implications.

Mathematical learning

In my experiments, I modelled the effects of tES on mathematical learning, as it provides a realistic model of everyday complex cognition, subserved by abilities that vary across and within individuals (Dowker, 2005, 2014), and if effective, offers potential intervention for up to 20% of the population who suffers from low numeracy and its associated life outcomes (Cohen Kadosh, Dowker, Heine, Kaufmann, & Kucian, 2013; Parsons & Bynner, 2005; Ritchie & Bates, 2013). Furthermore, as mathematical abilities deteriorate from the age of 50 (Hartshorne & Germine, 2015), the development of interventions are timely, especially that the growing aging population is predicted to have longer life expectancy.

Within the field of numerical cognition, it is generally agreed that mathematical abilities are subserved by "core"- and "non-core" skills [for a review, see (Looi & Cohen Kadosh, 2016)] that are mainly implicated in the dorsolateral prefrontal cortices (dlPFCs) and parietal cortices (PPCs) (Arsalidou & Taylor, 2011). Core skills are those typically considered as the “innate” or inherited capacities to understand and discriminate quantities, shared by human infants (Xu & Arriaga, 2007; Xu & Spelke, 2000) and other species (Cantlon & Brannon, 2006). Although, some core skills are acquired through schooling (Geary, Frensch, & Wiley, 2000). Non-core skills are those that are important for mathematical cognition, but not exclusive to the mathematical domain such as executive functions (inhibitory control, working memory, WM), spatial skills and attention (Passolunghi & Lanfranchi, 2012). With age, a fronto-parietal shift in activation has been observed (Rivera, Reiss, Eckert, & Menon, 2005), possibly reflecting the shift of reliance from more domain-general, non-core skills to more specialised, core skills. Crucially, these skills are trainable, which suggests that mathematical learning could be optimised. To date, most mathematical training studies have focused on core skills, such as basic numerical representation, compared to non-core skills such as attention [for a review, see (Looi & Cohen Kadosh, 2016)]. Based on the few studies that directly compared core and non-core skill training, it appears that training on core skills might be more effective in improving mathematical skills than training on non-core skills such as WM and language (Kuhn & Holling, 2014; Obersteiner, Reiss, & Ufer, 2013).

Core skills are those specific to mathematical abilities such as automaticity in processing numerical information, the ability to discriminate numerosities, represent numerosities and counting (Butterworth, 2010). They serve as the foundation for schooling and later mathematics achievement (Barth, Beckmann, & Spelke, 2008; De Wind & Brannon, 2012; Dehaene, 2009; Feigenson, Libertus, & Halberda, 2013), and are impaired amongst individuals with mathematical learning disabilities (Mazzocco, Feigenson, & Halberda, 2011; Rubinsten & Henik, 2009). These skills are supported by the approximate number system (ANS) and the exact number system (ENS) (Feigenson, Dehaene, & Spelke, 2004). The ANS is characterised by increasing imprecision in the representation of numbers with increasing absolute numerical value (Gallistel & Gelman, 1992), and the ENS is associated with the precise representation of numbers for comparison and manipulation of quantities using symbols. While increased precision in representation of numbers is commonly observed with schooling and attributed to the acquisition of numerical symbols (Mussolin, Nys, Content, & Leybaert, 2014; Verguts & Fias, 2004), processes that contribute toward such refinement remain unclear (Mussolin, Nys, Leybaert, & Content, 2016). Training studies that examine the relationship between non-symbolic and symbolic representation might reveal practical implications for the development of learning materials and interventions.

To date, studies on core skills have focused on ANS rather than ENS using tasks such as number line mapping (Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger, Gälli, et al., 2011; Link et al., 2013), numerosity discrimination (De Wind & Brannon, 2012), and approximate addition and subtraction (J. Park & Brannon, 2013; Praet & Desoete, 2014). Weeks, if not months of such intensive training have shown improvements on trained tasks, but mixed findings of transfer effects. For example, while some studies found transfer effects beyond trained domains (Hyde, Khanum, & Spelke, 2014; Link et al., 2013; Obersteiner et al., 2013; J. Park & Brannon, 2013), others did not (Aunio, Hautamäki, & Van Luit, 2005; De Wind & Brannon, 2012). Similarly, there were inconsistent findings on the long-term effects of training. While some found sustained effects 5-6 weeks post-training (Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger, & von Aster, 2011; Praet & Desoete, 2014), others did not [e.g., (Aunio et al., 2005)]. Converging findings suggest that optimisation of numerical training tasks might promote better learning and transfer effects; for example, the use of tasks that are engaging, such as those that are gamified, adaptive, provide feedback (Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger, & von Aster, 2011), and involve bodily movements (Fischer, Moeller, Bientzle, Cress, & Nuerk, 2011; Link et al., 2013; Moeller et al., 2012). In a parallel line of study, the use of tES as an adjuvant to numerical training has also shown to promote better performance than training alone, with transfer and long-term effects [(Cappelletti et al., 2013; Cohen Kadosh et al., 2010; Snowball et al., 2013) for a review on mathematical training and brain stimulation, see (Looi & Cohen Kadosh, 2016)]. However, given that the majority of mathematical training studies have been based on healthy children, and tES studies on healthy young adults (Looi & Cohen Kadosh, 2014, 2016), further research should extend the investigation of tES and training effects into atypical populations, and older populations.

In sum, the fields of cognitive training, mathematical training and tES that share the pursuit to enhance human learning and cognition also share the challenge of translating of laboratory findings for real-life applications. One direction to improve training and transfer outcomes is to improve the ecological validity of training tasks. Given individual differences and changes in the level of neuroplasticity and cognition across the lifespan, there is a need to examine and understand training effects in typical and atypical populations, across different ages to improve learning and cognition of the individual and for all.

Research questions

In the current thesis, I used more realistic training tasks to explore the effects of cognitive training alone (on healthy children), and the combination of cognitive training and brain stimulation compared to training alone in typical (healthy adults and elderly) and atypical populations (children with learning disabilities). I examined the following questions:

1. Would cognitive training alone on a computer-based training improve numerical learning of healthy children? (See Chapter 1)
2. Would combining tES with a numerical video game enhance numerical learning and long-term transfer of healthy adults? (See Chapter 2)
3. Would combining tES with a numerical video game improve numerical learning and transfer of children with mathematical learning disabilities? (See Chapter 3)
4. Would combining tES with an iPad numerical game improve numerical learning and transfer of older adults? (Chapter 4)

Chapter 1

Improving children's numerical learning using a computer-based cognitive training

Abstract

Mathematical achievement that has enduring impact on an individual's life outcomes is linked with the ability to represent numerical magnitude. Indeed, the few training studies on locating quantities on a line, or 'number line mapping' have shown transfer effects to improved mathematical skills. However, as previous studies included mapping of both symbolic and non-symbolic quantities in the same task, it is unclear whether, and how training on these different formats might affect numerical learning. In the current study, I directly compared the effects of computer-based training on mapping symbolic (Arabic digits) vs. non-symbolic (dots) representation onto a virtual number line. Children (n=36) aged 7-9 years old were pseudo-randomly assigned to either Dots or Digits group, and trained for 15 days of 20 minutes each session at school. I found that the Digits group was more accurate in mapping than the Dots group, and showed improved accuracy with training. Consistent with previous studies, I found that mapping accuracy across groups was significantly correlated with mathematical achievement. However, across and within groups, mapping accuracy did not predict mathematical achievement and vice versa, and training progress was not correlated with change in mathematical achievement. Optimisation of training task and transfer measures is needed to disentangle the contribution of symbolic vs. non-symbolic mapping to individual mathematical achievement.

Introduction

Mathematical skills and achievement at a young age predicts life outcomes in adulthood (Ritchie & Bates, 2013). Hence, understanding ways to promote better learning and achievement at a young age could have significant implications for the individual and society. One promising approach that is cost-effective, accessible to individuals across different socioeconomic backgrounds, and engaging is cognitive training.

Cognitive training has shown the potential for improving the numerical learning of typically developing children (Kuhn & Holling, 2014; Obersteiner et al., 2013; Rauscher et al., 2016) and those with mathematical learning disabilities (Käser et al., 2013; Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger, Gälli, et al., 2011; Räsänen, Salminen, Wilson, Aunio, & Dehaene, 2009; A. J. Wilson, Revkin, Cohen, Cohen, & Dehaene, 2006) [for a review see, (Cohen Kadosh et al., 2013; De Smedt, Noël, Gilmore, & Ansari, 2013)]. In particular, training using computer-based games offers an ecological approach that is engaging, and flexible to manipulations for personalised learning and experimental purposes (Käser et al., 2013; Moeller, Fischer, Nuerk, & Cress, 2015; Moreau & Conway, 2014). As computer-based training tasks could be easily customised and there is a variety of approaches to training [for a review, see (Jolles & Crone, 2012)], optimising the content of training is key to promoting the desired learning effects and outcomes.

Within the numerical domain, training that is focused on domain-specific skills such as numerical magnitude representation appear to promote better numerical skills than domain-general skills such as working memory, WM (Kuhn & Holling, 2014) and language (Obersteiner et al., 2013). Within domain-specific skills, training on numerical magnitude representation through number line mapping [locating the corresponding position of a combination of dots, Arabic digits, approximate addition and subtraction on a number line; (Käser et al., 2013; Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger, Gälli, et al., 2011; Rauscher et al., 2016), for a review of number line training studies, see (Moeller et al., 2015)], has been linked with improved numerical skills, and changes at the neural level (Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger, Gälli, et al., 2011). However, given that the association between numerical magnitude processing and mathematics achievement is influenced by the format of representation, i.e., non-symbolic vs. symbolic [see review based on correlation and regression studies that are mostly based on number comparison tasks, (De Smedt et al., 2013)], and the recent view that they are based on different mechanisms (Gebuis, Cohen Kadosh, & Gevers, 2016), it is unclear how training on these formats separately on the number line might affect numerical representation and learning. Furthermore, while more precise numerical representation with schooling is attributed to the acquisition of symbolic representation (Arabic digits) (Mussolin et al., 2014; Verguts & Fias, 2004), little is known about the processes that support such refinement (Mussolin et al., 2016).

In the current study, I investigated whether computer-based cognitive training on mapping non-symbolic (dots) and symbolic (Arabic digits) separately on a virtual number line would (1) result in different mapping performance and learning; and (2) affect the relationship between mapping performance and mathematical achievement. Typically developing children (n=36) aged 7-9 years old trained on the game ‘Calcularis’ (Käser et al., 2013; Rauscher et al., 2016) for 20 minutes every day, 5 days per week for 3 weeks at school. I administered cognitive assessments (mathematical achievement, WIAT-II UK; reading abilities, TOWRE; and working memory, Digit Span, Letter Span and Corsi Blocks) before and after training. Children were pseudo-randomly assigned to train on either mapping dots (Dots group) or digits (Digits group) based on a range of variables (Table 1). Training was focused on number line mapping because it does not require knowledge of measurement units of entities, is ecologically valid, as it is taught in school, and is a relatively straightforward measure of numerical representations and changes in performance with experiences, such as learning (Siegler & Booth, 2004). I measured the mapping performance and learning using dots vs. digits (accuracy, RT, pattern and variability), and examined the relationship between mapping accuracy and mathematical achievement. Based on previous correlation and regression studies using different tasks [see (De Smedt et al., 2013) for a review], I hypothesised that: (1) mapping performance and learning would be better using digits than dots; (2) individual mapping accuracy is related to mathematical achievement; and (3) changes in mathematical achievement would be related to training with digits.

Method

Participants

Thirty-six children were recruited from a primary school in Oxford (20 girls; between 7.3– 9.1 years old, mean ± one standard error of the mean: 96.2±1.1 months at the first point of study). Children were in their Year 3 (24; 11 girls) and Year 4 (12; 9 girls) [Note that difference in gender between Year groups were not significant; $\chi^2(1)=2.8$, $p=.1$]. Parents gave written consent and children gave their informed assent before taking part in this study. The Medical Sciences Research Ethics Committee (MSD-IDREC-C1-2012-107) gave ethical approval for this study.

Computer-based training

All children played 'Calcularis', a number line mapping game at school in groups of 6 (2 groups of Year 3; 1 group of Year 4 per training batch x 2) for 20 minutes per day, 5 days a week for 3 weeks. This computer-based game features mapping dots or digits onto a virtual number line with identical overall design to that of (Käser et al., 2013; Rauscher et al., 2016). Children were pseudo-randomly assigned to 2 groups, either mapping Arabic digit(s) (Digits group) or dots (Dots group) based on their mathematical performance and year group, as well as a range of other cognitive baseline performance (Table 1). Every trial allows about 20 seconds for children to decide and map the location of the Arabic digit or dots onto the number line before a falling cone reaches the number line (Figure 1). Children used the arrow keys (left or right) on laptops for the mapping. The game provides visual feedback by zooming into the correct location of the Arabic digit or dots on the number after response is given in every trial.

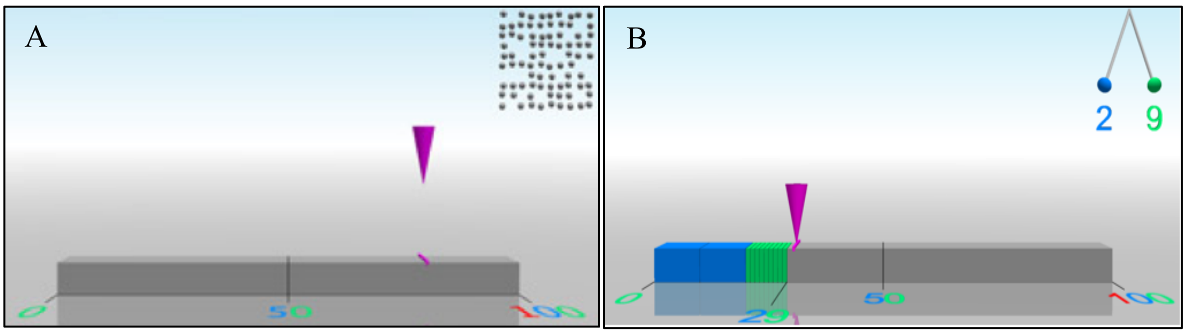

Figure 1 Computer-based cognitive training on number line mapping using A) dots and B) Arabic digits. Every trial allows about 20 seconds for children to map the

location of the Arabic digit or dots onto the number line using arrow keys (left or right) on laptops. Feedback with a visual zoom into the correct location for the Arabic digit or dots is given after every trial.

Controlled variable	Digits group	Dots group	Differences between groups
Age (months) Mean (SD)	96 (6.9)	96.9 (5.9)	t(33)=.41, *p*>.68
Year	12 Year 3, 6 Year 4	12 Year 3, 6 Year 4	$\chi^2(1)=0$, *p*=1
Gender	9 boys, 8 girls	7 boys, 11 girls	$\chi^2(1)=0.7$, *p*=.40
Mathematical abilities Mean (SD)			
WIAT	106.3 (14.9)	102.8 (14.2)	t(32)=.71 *p*>.49
Numerical Operations	107.9 (13.6)	104.8 (12.8)	t(32)=.69 *p*>.50
Mathematical Reasoning	103.6 (12.8)	100.7 (14.2)	t(32)=.62 *p*>.54
Reading proficiency (TOWRE) Mean (SD)			
Sight word	109.4 (9.8)	106.0 (18.5)	t(33)=.66, *p*>.51
Phonemic	109.9 (14.0)	108.8 (18.6)	t(33)=.19, *p*>.85
Working memory (WM) Mean (SD)			
Verbal (Digit Span)			
Forward	4.53 (1.13)	4.44 (.78)	t(33)=.26, *p*>.80
Backward	2.59 (.71)	2.61 (.61)	t(33)=-.10, *p*>.92
Verbal (Letter Span)			
Forward	3.47 (.94)	3.67 (.84)	t(33)=-.65, *p*>.52
Backward	2.47 (.62)	2.61 (.85)	t(33)=-.55, *p*>.58
Visuospatial (Corsi Blocks)			

Forward	3.41 (.87)	3.83 (.62)	t(33)=-1.67, *p*>.11
Backward	2.94 (.66)	3.11 (.96)	t(33)=-.61, *p*>.55

Table 1 Typically developing children were matched across groups (Dots vs. Digits) based on a range of baseline cognitive performance. Table shows the standard scores. Note that for WIAT, one child (from the Dots group) did not have a standard score for mathematical performance due to underperformance below a certain level in the WIAT at pre-test, and was excluded from the following analyses.

Cognitive assessments

I administered cognitive tests before and after cognitive training. I assessed children on their mathematical achievement, reading abilities, and working memory (WM) capacity. Mathematical achievement was assessed using the Wechsler Individual Achievement Test, 2nd Edition, UK (WIAT-II, UK). Children were assessed on their competency on both numerical operation and mathematical reasoning. Reading abilities was assessed using Test of Word Reading Efficiency (TOWRE-2, Pearson) on both sub-tests of Sight Word Efficiency and Phonemic Decoding Efficiency. Sight Word Efficiency measures the number of real words an individual could accurately identify on printed, vertical lists within 45 seconds. The Phonemic Decoding Efficiency assessed the number of phonemically regular non-words an individual can accurately decode within 45 seconds. Including time for directions and practice items, each test took approximately 5 minutes. Children were assessed on their WM capacities using the Digit Span, Letter Span and Corsi Blocks tasks. The Digit Span and Letter Span tasks assess verbal WM capacity using digits and letters respectively. I read aloud a series of digits and each child was asked to repeat the sequence in the forward order. The first trial consisted of 2 digits, the span of each trial increases by 1 digit with every 2 trials. This task took about 5 minutes, and is repeated with the instruction to repeat the digits in the backwards order. The Corsi Blocks task assesses visuospatial WM capacity. I tapped on a series of blocks and each child was instructed to tap the same sequence on the blocks. The first trial consisted of a sequence involving 2 blocks, and with every 2 trials, the sequence increases with an additional block. This task took about 5 minutes, and was repeated with the instruction to repeat the block sequence in a backwards order.

Procedure

I conducted cognitive assessments and training following the procedure in Figure 2 below.

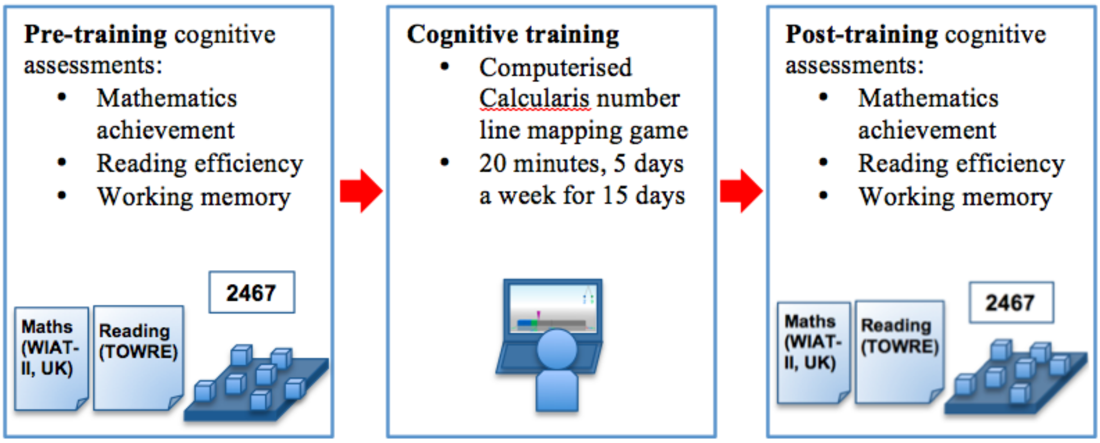

Figure 2 Summary of experimental procedure

Statistical analyses

I used IBM SPSS Statistics to perform all statistical analyses, with the threshold for significance set at $p<.05$. I analysed computer game mapping accuracy, mean RT, and cognitive assessments (mathematical, reading and WM abilities) by running Analysis of Variance (ANOVA). Game accuracy was defined as percent absolute error [Absolute deviation from Target/Number range*100], similar to previous studies (Rauscher et al., 2016; Siegler & Booth, 2004). Trials were considered as outliers and not considered for analyses if they exceed 25 seconds (performance above 25 seconds were likely to have included pauses triggered by pressing on the 'spacebar' on the keyboard), or were ±3SD from the mean percent absolute error of each subject. Together, these trials accounted for 7.5% of all trials. All training data was uploaded automatically to a server during training period, and was later downloaded from the server when training ended for statistical analyses. Due to server upload failure of training data, the current analyses included data up to Day 11 to account for the maximal number of participants from each group possible (n=31; Dots=15; Digits=16). However, I provide the interaction and effect sizes up to Day 15 in Tables 2 and 3, which shows similar patterns to those up to Day 11. Note that n=31 given the exclusion of 1 subject from the Dots group for underperforming in WIAT, and 1 from the Digits group due to failure of data retrieval from server, and missing cognitive assessment data of 3 subjects (Digits=2; Dots=1).

Results

Training performance

Accuracy

I ran a 2-way ANOVA on Time (Day 1-11) x Group (Digits, Dots) on percent absolute error (see *Statistical Analyses* for details). I found that the interaction between Time and Group was significant [F(10,290)=2.61, MSE=1.23, p=.005, η^2_p=.082]. This was due to significantly more accurate mapping of the Digits group than the Dots group on all days of training (all p<.001; see Figure 3). Results were consistent when accounting up to 14 days of training (see Table 2). Within groups, the Digits group showed a significant main effect of Time [F(10,150)=7.87, MSE=.51, p<.001, η^2_p=.34; 60% of variance was explained by linear trend p<.001], while the Dots group did not show a significant main effect of Time [F(10,140)=1.22, MSE=2.00, p=.28, η^2_p=.08]. This suggests that those in the Digits group were not only more accurate in mapping compared to the Dots group on each training day, but they also improved and became more accurate in mapping with training (Figure 3).

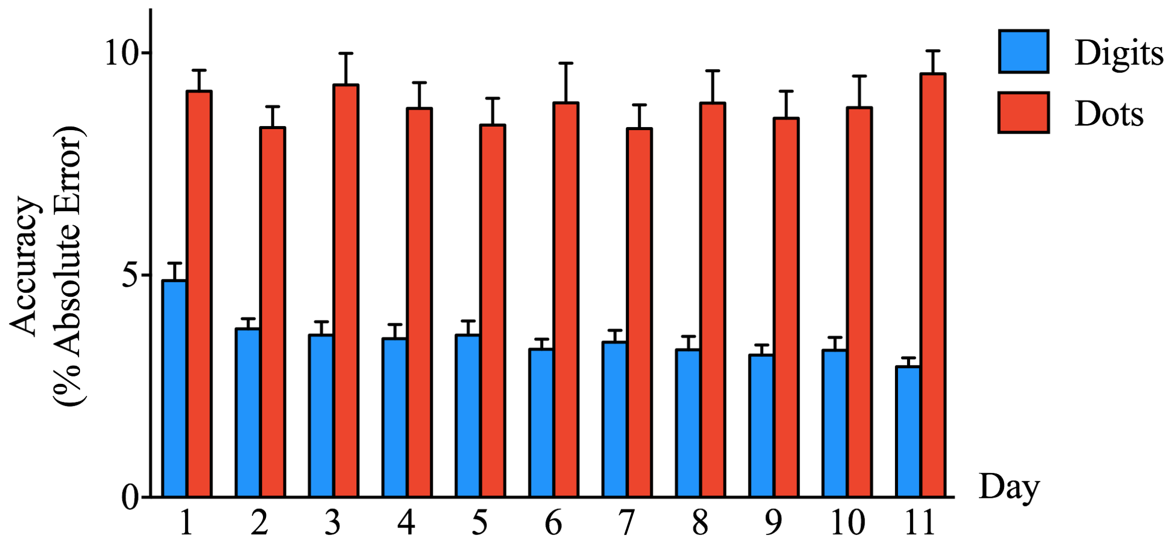

Figure 3 Interaction between Day and Group in accuracy of mapping. The Digits group was significantly more accurate in mapping across all training days compared to the Dots group, and showed a significant improvement with training.

Days (participants, n)	Time x Group interaction (Accuracy)
12 (Dots=15; Digits=15)	$F(11,308)=2.47$, $MSE=1.23$, $p=.006$, $\eta^2_p=.081$
13 (Dots=15; Digits=14)	$F(12,324)=2.06$, $MSE=1.27$, $p=.019$, $\eta^2_p=.071$
14 (Dots=15; Digits=13)	$F(13,338)=1.73$, $MSE=1.33$, $p=.054$, $\eta^2_p=.062$
15 (Dots=15; Digits=5)	$F(14,252)=1.10$, $MSE=1.65$, $p=.36$, $\eta^2_p=.057$

Table 2 Time and Group interaction in Accuracy. Results were consistent up to 14 days of training. Note the increasing effect size with increasing number of participants. Due to server upload failure, training data of 11 children on Day 15 were lost (all from Digits group, indicating that upload failure affected most children from the same group who trained on the same day).

Response Times

I ran a 2-way ANOVA on Time (Day 1-11) x Group (Digit, Dots) on mean RT. I found that the interaction between Time and Group was not significant [$F(10,290)=1.08$, $MSE=.53$, $p=.38$, $\eta^2_p=.04$] (results were consistent up to 13 days of training, Table 3). The main effect of Time was significant [$F(10,290)=28.88$, $MSE=.53$, $p<.001$, $\eta^2_p=.50$; 62% of variance was accounted by linear trend] indicating that across groups, there was an increase in mean RT with training. Such increase in mean RT was not a trade-off due to improved accuracy ($r=.1$, $p=.59$). Further studies are needed to examine if this was due to reduced attention or motivation during training. From my observation, it appeared that children were more excited at the beginning of the game and might have pressed on the arrow keys for a prolonged period to speed up the falling of the cone on the number line and hence, produced quicker responses.

Day (participants, n)	Time x Group interaction (mean RT)
12 (Dots=15; Digits=15)	$F(11,308)=1.48$, $MSE=.53$, $p=.14$, $\eta^2_p=.050$
13 (Dots=15; Digits=14)	$F(12,324)=1.44$, $MSE=.51$, $p=.15$, $\eta^2_p=.051$
14 (Dots=15; Digits=13)	$F(13,338)=1.83$, $MSE=.52$, $p=.037$, $\eta^2_p=.066$
15 (Dots=15; Digits=5)	$F(14,252)=1.73$, $MSE=.58$, $p=.05$, $\eta^2_p=.088$

Table 3 Time and Group interaction in mean RT. Results were consistent up to 13 days of training.

Patterns of mapping

Logarithmic vs. Linear

Based on Siegler and Booth (2004), I examined the patterns of children mapping across the Dots and Digits groups. I examined whether each group's median estimates were better fitted by the logarithmic (log) or linear function. I used the median instead of mean estimates to reduce the effects of outliers, similar to Siegler and Booth (2004). To compare the absolute value of the difference between the median of children's of children's estimates for each number and the prediction for that number generated by (a) the best fitting linear model and (b) the logarithmic model, I conducted paired-sample *t*-tests between these differences. The best fit is determined by the function with the least difference from children's median estimates. I found that across groups, the linear model best fits children's mapping (Figure 4). Notably, there were smaller differences between the median estimates and the values predicted by the linear model compared to the log function. I report the results in Table 4. This pattern is consistent with that reported on children of the same age by Siegler and Booth (2004).

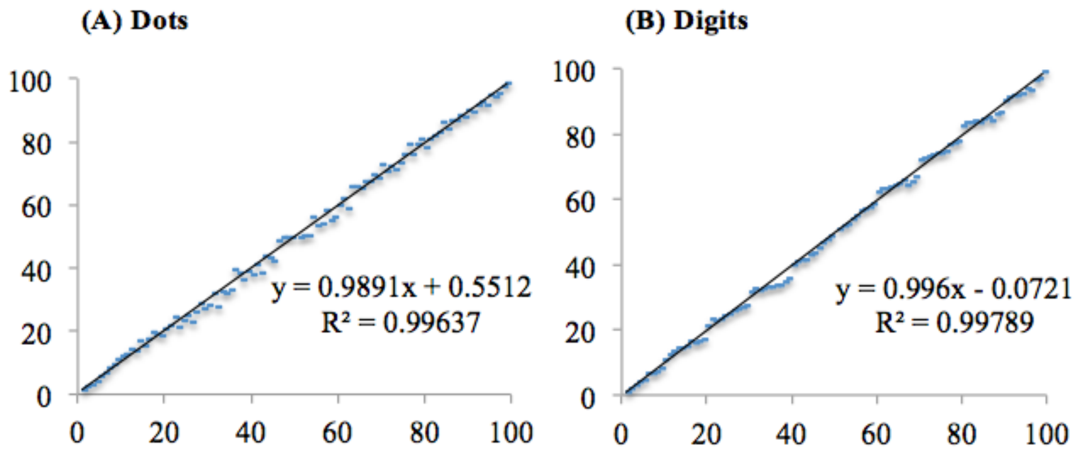

Figure 4 Patterns of mapping. Linear mapping of children in A) Dots and B) Digits Dots group (median estimates as a function of target).

Group	Linear fit (%)	Log fit (%)	Difference between estimates of median and functions	Best fit
Digits	99.89	89.46	t(97)=-16.37, *p*<.001, Cohen's d=.34	Linear
Dots	99.82	89.30	t(97)=-16.37, *p*<.001, Cohen's d=.34	Linear

Table 4 Fitting of linear and logarithmic fit for Dots and Digits groups. Note that Targets n=98, as the target and responses for number 50 and 100 were removed, given that the 'mapping cone' was dropped automatically and directly above the position of 50 on the number line, and the position of 100 was marked by the Arabic digit, 100, biasing accuracy of responses.

Variability

I further examined the pattern of variability in each group using the standard deviation of mapping as a function of target number/dot(s) [(Ebersbach et al., 2008)(Figure 5)]. The variability of number mapping (Arabic digits) of children between 5 to 9 was previously shown to depend on anchors on the number line (Ebersbach et al., 2008). Specifically, the variability of estimations in the middle range (i.e., around the value of 50 for a number range between 0-100) is the highest when children took externally depicted lower and upper anchor into account. Current findings on the Dots group replicated this pattern (Figure 5A); I found strong negative correlations between standard deviation of children's mapping of each target and the absolute differences between targets and the midpoint, 50 (r=-.87, *p*<.001).

Of interest, I found that the variability of mapping of children from the Digits group resembled an 'm'-shape (Figure 5B), with lower deviations at either ends of the anchors (0 and 100), and on either side of the number line's mid-point (50; see Figure 3), unlike the inverted 'U'-shape when mapping dots onto the number line. This suggests that when children were mapping digits on the number line, they used the anchor, 50 improve the accuracy of mapping. Indeed, I found strong negative correlations between standard deviation of children's mapping of each target and the absolute differences between targets and the new mid points, 25 (r=-.82, *p*<.001) and 75 (r=-.77, *p*<.001) in the Digits group.

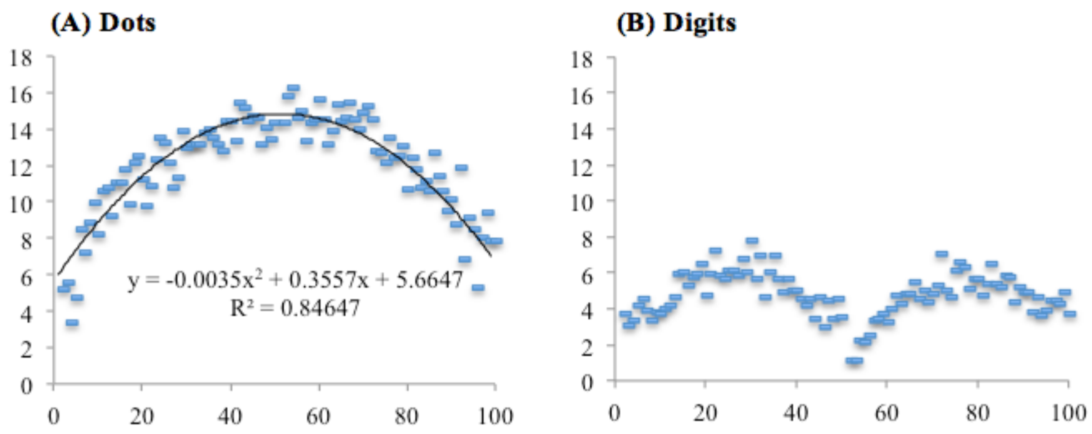

Figure 5 Variability in mapping. Patterns of variability in mapping of children in the A) Dots and B) Digits group (standard deviation of mapping as a function of target). The 'm'-shape pattern shown by the Digits group suggests that the use of symbolic representation (Arabic digits) enabled more accurate and effective anchoring strategy (the addition 50 as an anchor), which increased the precision of number line mapping.

Cognitive Tasks

Mathematical achievement (WIAT)

I conducted a 3-way ANOVA on Task (Numerical Operations, Mathematical Reasoning) x Time (pre-training, post-training) x Group (Digit, Dots). The main effect of Time was significant [$F(1,29)=58.35$, $MSE=54.53$, $p<.001$, $\eta^2_p=.67$], indicating higher scores across tasks at post-training than at pre-training [$t(30)=-7.75$, $p<.001$; pre-training: 103.11±11.64 vs. post-training: 113.27±10.56]. The main effect of Task was also significant [$F(1,29)=5.49$, $MSE=74.63$, $p=.026$, $\eta^2_p=.16$], indicating higher scores in Numerical Operations than Mathematical Reasoning [$t(30)=2.38$, $p=.024$; Numerical Operations: 110.03±SD=12.21 vs. Mathematical Reasoning:

106.35±SD=10.39]. The main effect of Group and interactions were not significant (all p>.35).

Reading abilities (TOWRE)

I conducted a 3-way ANOVA on Task (Sight Word, Phonemic) x Time (pre-training, post-training) x Group (Digit, Dots). I found that the main effect of Time was significant [F(1, 29)=9.0, MSE=33.40, p=.005, η^2_p=.24], suggesting that scores across tasks were higher at post-training than pre-training [t(30)=-3.06, p=.005; pre-training: 105.98±SD=12.92 post-training: 109.11±SD=13.61]. All other main effects and interactions were not significant (all p>.26).

Working memory capacity

I conducted a 4-way ANOVA on Task (Digit Span, Letter Span, Corsi Blocks) x Order (Forward, Backward) x Time (pre-training, post-training) x Group (Digit, Dots). I found that there was a significant interaction between Task and Order [F(2,58)=22.33, MSE=.364, p<.001, η^2_p=.44]. This stemmed from higher number of items recalled in the forward order in the Digit Span [t(30)=17.18, p<.001], Letter Span [t(30)=8.07, p<.001] and Corsi Block [t(30)=5.44, p<.001]. Within the forward order, there was significantly higher number of items recalled in Digit Span task (4.42±SD=.71) compared to Letter Span (3.60±SD=.70) [t(30)=7.64, p<.001] and Corsi Blocks tasks (3.74±SD=.59) [t(30)=-4.65, p<.001]. Within the backward order, there was significantly higher number of items recalled in the Corsi Blocks task (3.10±SD=.47) compared to Digit Span (2.76±SD=.53) [t(30)=-2.57, p=.015] and Letter Span tasks (2.58±SD=.59) [t(30)=-4.33, p<.001]. The main effect of Group, Time and other interactions were not significant (all p>.29).

Training and transfer

The improvements found in mathematical and reading abilities from pre- to post-training might reflect the test-retest effects (repetition of the same tests in a relatively short amount of time), rather than the effect of cognitive training. Of particular interest, I examined whether improved accuracy in the current training generalised to *other* cognitive domains that showed changes from pre- to post-training (mathematical achievement, reading ability), I correlated the training gains with post-training scores controlled by pre-training scores, as this method has been recommended as more suitable than the subtraction method given the current experimental design; I assigned participants into groups based on their performance at pre-training where their scores did not differ (Edwards, 2001; Van Breukelen, 2006) (Table 1).

Mathematical achievement

I found that the correlation between the gain in accuracy vs. post-training WIAT scores, controlled for pre- training WIAT scores was not significant for the Digits ($r=-.29$, $p=.30$) or the Dots group ($r=-.15$, $p=.61$).

Reading abilities (TOWRE)

I found that the correlation between the gain in accuracy vs. post-training TOWRE composite scores, controlled for pre- training TOWRE composite scores was not significant for the Digits ($r=.27$, $p=.34$) or the Dots group ($r=-.11$, $p=.70$).

Together, the lack of association with training indicates that the improvements observed in mathematical and reading abilities as a function of time might be attributed to test-retest effect, rather than the improvement in the accuracy of current training.

Mapping accuracy and mathematical achievement

Across groups, the accuracy of number line mapping on Day 1 was significantly correlated with pre-training WIAT scores (r=-.38, p=.037). This relationship remained significant when I controlled for Groups (r=-.54, p=.002), supporting the relationship between numerical line estimation and mathematical achievement (Siegler & Booth, 2004).

I further examined whether individual differences in pre-training WIAT achievement across groups is linked with mapping accuracy later in the training. I ran a partial correlation between pre-training WIAT scores and the accuracy of Day 11, controlling for Day 1 accuracy on all participants. I did not find a significant correlation (r=.23, p=.21). Results were consistent when I correlated the pre-training WIAT scores with gain (Day 11-1 Accuracy), controlled for Day 1 accuracy (r=.23, p=.21).

I also investigated whether individual differences in the accuracy of mapping across groups on Day 1 is associated with post-training WIAT scores (Siegler & Booth, 2004), I conducted a partial correlation between Day 1 accuracy and post-training WIAT scores, controlled for pre-training WIAT training scores. I did not find a significant correlation (r=-.02, p=.91).

As the consistency of the relationship between numerical magnitude processing and mathematical achievement was shown to differ according the number format used (De Smedt et al., 2013), I ran moderation analyses to examine if Group (Digits, Dots) influenced this relationship. I found that Group did not significantly moderate the relationship between Day 1 mapping accuracy post-training WIAT scores, when controlled for pre-training WIAT scores, as the interaction between Group and Day 1 Accuracy was not significant, $p>.16$. Similarly, Group did not significantly moderate the relationship between pre-training WIAT scores and Day 11 mapping accuracy, when controlled for Day 1 mapping accuracy, as the interaction between Group and Day 1 Accuracy was not significant, $p>.74$.

Together, these findings suggest that while number line mapping accuracy across groups (Digits, Dots) is linked with mathematical achievement at pre-training, the initial mapping accuracy was not associated with later mathematical achievement, initial mathematical achievement was not associated with later mapping accuracy, and training progress was not correlated with change in mathematical achievement across or within groups, when assessed after training.

Discussion

In the current study, I investigated whether (1) and how mapping dots or digits on the number line would promote different mapping performance and learning; and (2) affect the relationship between mapping performance and mathematical achievement.

I found that the mapping performance and learning differed between mapping dots and digits on the number line. As predicted, those from the Digits group were more precise than those from the Dots group in number line mapping, demonstrating the impact of access to numerical symbols on the acuity of numerical representation [for review, see (Mussolin et al., 2016)]. Furthermore, while those in the Digits group showed improved precision in numerical mapping with training, it was not the case for the Dots group. Further analyses suggest that while both groups showed linear rather than logarithmic fit in mapping, in line with previous findings on the same age group (Siegler & Booth, 2004), the more precise mapping of the Digits group compared to the Dots group might be explained by the use of better anchoring strategy with the use of symbols as indicated by variability (SD) in mapping. Specifically, the current findings indicate that children from the Digits group employed the use of additional (mentally assigned) anchor, 50 (apart from 0 and 100), which served as the upper (≤50) or lower limit (≥50) to narrow down the number range of potential mapping locations, hence improving mapping accuracy compared to the Digits group (that employed anchors of 0 and 100). Therefore, one of the processes that contribute towards the refinement of the magnitude representation (or ANS) after the acquisition of numerical symbols (Arabic digits) (Mussolin et al., 2016) might be the use of additional, more precise anchors on the number line to form a more linear magnitude representation with equal spacing between numbers, and less overlap between magnitude representation.

Notably, I did not find any transfer effects from training gains (accuracy) to mathematical achievement, reading abilities or WM capacities. While I found that the initial mapping accuracy was significantly correlated with mathematical achievement across Digits and Dots groups, consistent with previous studies [e.g., (Sasanguie, Van den Bussche, & Reynvoet, 2012; Siegler & Booth, 2004)], mapping accuracy was not linked with later mathematical achievement, and initial mathematical achievement was not linked with later mapping accuracy, across and within groups. Training progress was not related to later mathematical achievement. As this is the first study that directly compared training on mapping using Dots vs. Digits on number line mapping, it is unclear whether the lack of transfer effects, especially to mathematical achievement, and link between mapping training and mathematical achievement might be influenced by differences in the training task design and type of tasks used to measure mathematical achievement compared to previous studies (De Smedt et al., 2013; Moeller et al., 2015).

In terms of training task, the current training design is not adaptive compared to previous number line training studies (Käser et al., 2013; Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger, Gälli, et al., 2011; Rauscher et al., 2016) and the more common number comparison studies (Kuhn & Holling, 2014; Obersteiner et al., 2013). Compared to non-adaptive training, adaptive training has been shown to produce better training and transfer gains in another cognitive domain [e.g., (J. Holmes et al., 2009)]. Future studies might consider integrating the adaptive feature in training to improve training and transfer outcomes. In addition, further studies might also consider integrating embodiment, or the use of body movements during training, as it has been shown to promote better training and transfer outcomes compared to computer-based training alone (Fischer et al., 2011; Link et al., 2013; Moeller et al., 2012). As you will see, I integrated these features to the design of my video game training used in the remaining experiments of this thesis.

In terms of tasks used to measure mathematical achievement, the use of WIAT-II UK might not be sensitive enough to detect specific transfer effects from training. In particular, it measures a broad range of mathematical skills with few questions that could be answered by children aged 7-9 compared to adults, yielding a total score that is averaged across various mathematical components, each based on few responses. As the link between mathematics achievement and numerical magnitude representations might rely on the specific mathematical skill under consideration, which might vary across different standardised achievement tests, more refined tasks closer to the training task, or curriculum-calibrated test are needed disentangle the associations between numerical magnitude representations and mathematical skills (Vanbinst, Ghesquiere, & De Smedt, 2012). Indeed, previous studies on number line training, although not directly comparable in terms of the content of training (mixed multi-representation training with the same overall design), have shown improvement in specific components of arithmetic [e.g., subtraction (Käser et al., 2013; Rauscher et al., 2016); subtraction and addition (Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger, Gälli, et al., 2011)], rather than general mathematical achievement on standardised tasks. Finally, as it is unclear whether training on dots and digits might have cumulative effects in the long run, studies that examine the long-term effects of training using digits and dots on the acuity of magnitude representation and other cognitive abilities are needed.

Overall, the current study suggests that symbolic representation promotes higher acuity of numerical magnitude representation compared to non-symbolic representation amongst primary school children. The use of symbols might have refined magnitude representation through more accurate and effective anchoring strategy, which improves with training. Consistent with previous correlation and regression studies, the initial mapping accuracy across symbolic and non-symbolic representation is associated with individual differences in mathematical achievement. Finally, optimisation of training and transfer tasks, and understanding of their differential effects is needed to understand the causality and direction of the relationship between mapping accuracy and mathematical achievement.

Chapter 2

Improving learning and cognition of the typical adult brain using a numerical video game and transcranial direct current stimulation[1]

Abstract

Cognitive training holds the potential for cheap, accessible and individualised learning, prevention of cognitive decline and rehabilitation. However, its application in the real-world is challenged by training design with little ecological validity, and inconsistent transfer and long-term effects. Since both cognitive training and tES modulate neuroplasticity, I investigated whether combining transcranial direct current stimulation (tDCS) with an engaging video game would further enhance training outcomes and promote transfer effects that are long-term. Healthy adults received active or sham tDCS over their dorsolateral prefrontal cortices (dlPFCs) during two days of 30-minute training each. Participants mapped fractions on a virtual number line by moving their body from side-to-side. Compared to the sham group, the active tDCS group showed better training outcomes, with transfer effects to an untrained domain. Moreover, tDCS-related gains were greater for those with lower baseline mathematical abilities, suggesting its potential for reducing cognitive inequalities. All effects remained 2-months later, suggesting the benefits of this combined approach for the long-term enhancement of learning and cognition amongst typical adults.

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[1] This chapter has been published as Looi et al. (2016) Combining brain stimulation and video game to promote long-term transfer of learning and cognitive enhancement. *Scientific Reports, 6*, 22003.

Introduction

Cognitive training could be a promising approach for individualized learning, prevention of cognitive decline and rehabilitation (Au et al., 2014a). However, its real-life implication is restricted by training design that lacked practical relevance, and inconsistent findings of transfer and long-term effects. In particular, weeks of training on simple tasks with little resemblance to realistic learning has resulted in a lack of transfer beyond the trained domain, and short-term gains (Melby-Lervåg & Hulme, 2013; van Heugten et al., 2016).

Meanwhile, the use of transcranial electrical stimulation (tES) has been shown to further improve training outcomes compared to training alone within 5-6 days (Cappelletti et al., 2013; Cohen Kadosh et al., 2010; Snowball et al., 2013). Similar to the field of cognitive training, findings of tES studies have been mostly based on simple training tasks. Furthermore, findings on its long-term effects have been inconsistent; some reported long-term effects for both trained and non-trained domains (Snowball et al., 2013), while others found long-term effects only for trained domains (Cappelletti et al., 2013). Given that both cognitive training and tES could modulate neuroplasticity, its synergy might promote greater transfer and long-term effects.

Of increasing relevance, individual differences have been shown to modulate the effects of cognitive training and tES. While cognitive training studies seemed to benefit those with higher cognitive abilities (Duncan et al., 2007; Lövdén, Brehmer, Li, & Lindenberger, 2012), tES appeared to benefit those with lower baseline abilities (Furuya, Klaus, Nitsche, Paulus, & Altenmüller, 2014; Sarkar et al., 2014;

Tseng et al., 2012). However, the reliability and generalisability of these results might be affected by the extreme groups approach, whereby participants were classified into groups within a cognitive ability (e.g., high vs. low) (Preacher, Rucker, MacCallum, & Nicewander, 2005). It is unclear how individual differences might influence the training outcome from combining cognitive training and tES.

In the current study, I combined the use of tDCS and a unique video game that I designed[2] to investigate whether the synergistic effects would result in greater training and transfer effects that are long-term. I also investigated if the training outcomes of this combined approach are influenced by participants' baseline mathematical performance. I set the training duration to an hour, as a previous study has shown neurophysiological changes from training after 2 hours (Sagi et al., 2012). I also chose a shorter duration to explore the potential of minimizing time commitment using a combined approach.

Healthy adults (n=20) were randomised to receive either 1mA bilateral (left: cathodal; right: anodal) active or sham tDCS to their dorsolateral prefrontal cortices (dlPFCs) during 2 days of 30-minute cognitive training each (Figure 1). I targeted the dlPFCs as they are known to be implicated in mathematical learning (Arsalidou & Taylor, 2011; Snowball et al., 2013; Zamarian, Ischebeck, & Delazer, 2009) and a range of domain-general, executive functions (Diamond, 2013). Given the overlapping networks (Reis et al., 2014), I inferred that the dlPFCs would be ideal stimulation sites to promote transfer effects. Specifically, I chose to apply the right-

[2] This video game was co-designed with my supervisor, Prof. Roi Cohen Kadosh, and prototyped by Dr. Mihaela Duta who developed the software. Both are co-authors on the published paper.

anodal, left-cathodal montage for several reasons: (1) A previous study showed that anodal tDCS to the left dlPFC with the reference electrode on the contralateral supraorbital region improved digit span performance that was specific to the forward order (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011). Meanwhile, repetitive transcranial magnetic stimulation (rTMS) at 1Hz over the right dlPFC to transiently disrupt its function impaired performance on both forward and backward digit span (Aleman & van't Wout, 2007). Note that contrasting rTMS at 1Hz, which has an interference effect, the anodal electrode in the current study that is assumed to facilitate cortical excitability was placed above the right dlPFC; (2) I adopted a bilateral instead of a unilateral tDCS montage (stimulating the contralateral dlPFC instead of using a reference electrode) because previous studies have reported more pronounced and specific effects using anodal tDCS in bilateral compared to unilateral tDCS (Mordillo-Mateos et al., 2012; Sehm, Kipping, Schäfer, Villringer, & Ragert, 2013; Vines, Cerruti, & Schlaug, 2008). Furthermore, another study showed that bilateral montage is more effective in producing localised current flows (Nathan, Sinha, Gordon, Lesser, & Thakor, 1993); and finally, (3) I chose the current montage instead of the opposite montage (right-cathodal, left-anodal) as the latter was found to impair learning in another numerical training paradigm (Iuculano & Cohen Kadosh, 2013).

Training was on an adaptive game that featured mapping fractions, a competence that was shown to predict mathematical achievement (Bailey, Hoard, Nugent, & Geary, 2012; Siegler & Booth, 2004). Participants mapped fractions on a virtual number line by moving their body from side-to-side, as embodiment during training has been linked with more pronounced training outcomes (Fischer et al., 2011; Link et al., 2013; Moeller et al., 2012). Moreover, the current video game was built on concepts from fields of neuroscience, psychology and education. Specifically, it was integrated with engaging features such as immediate feedback, difficulty levels that automatically adapt to individual performance, and complexity (computing and mapping fractions compared to simpler tasks such as numerosity discrimination), to increase its usability and attractiveness for real-life learning. The game recorded participants' response times (RT) and accuracy. Participants received either sham tDCS for 30 seconds, or active tDCS from a wireless cap throughout video game training for 30 minutes. To assess whether training effects were specific to the current video game (i.e., independent of tDCS), I further recruited an active control group (n=10); they received tDCS with the identical parameters to the active tDCS group throughout their performance on non-mathematical visuospatial tasks. To assess for long-term effects, I conducted a follow-up session 2 months later, and asked participants to perform on their previously assigned tasks (video game or visuospatial tasks) without tDCS. To examine training effects, transfer effects (working memory), and longevity of all effects, I collected data from participants before, immediately after, and 2 months after training.

I hypothesized that; 1) the active tDCS group would show better training outcomes than the sham tDCS group, with long-lasting improvements; 2) transfer effect would be specific to the active tDCS group who trained on the current video game; and 3) the effects of tDCS would differ depending on participants' baseline mathematical achievement.

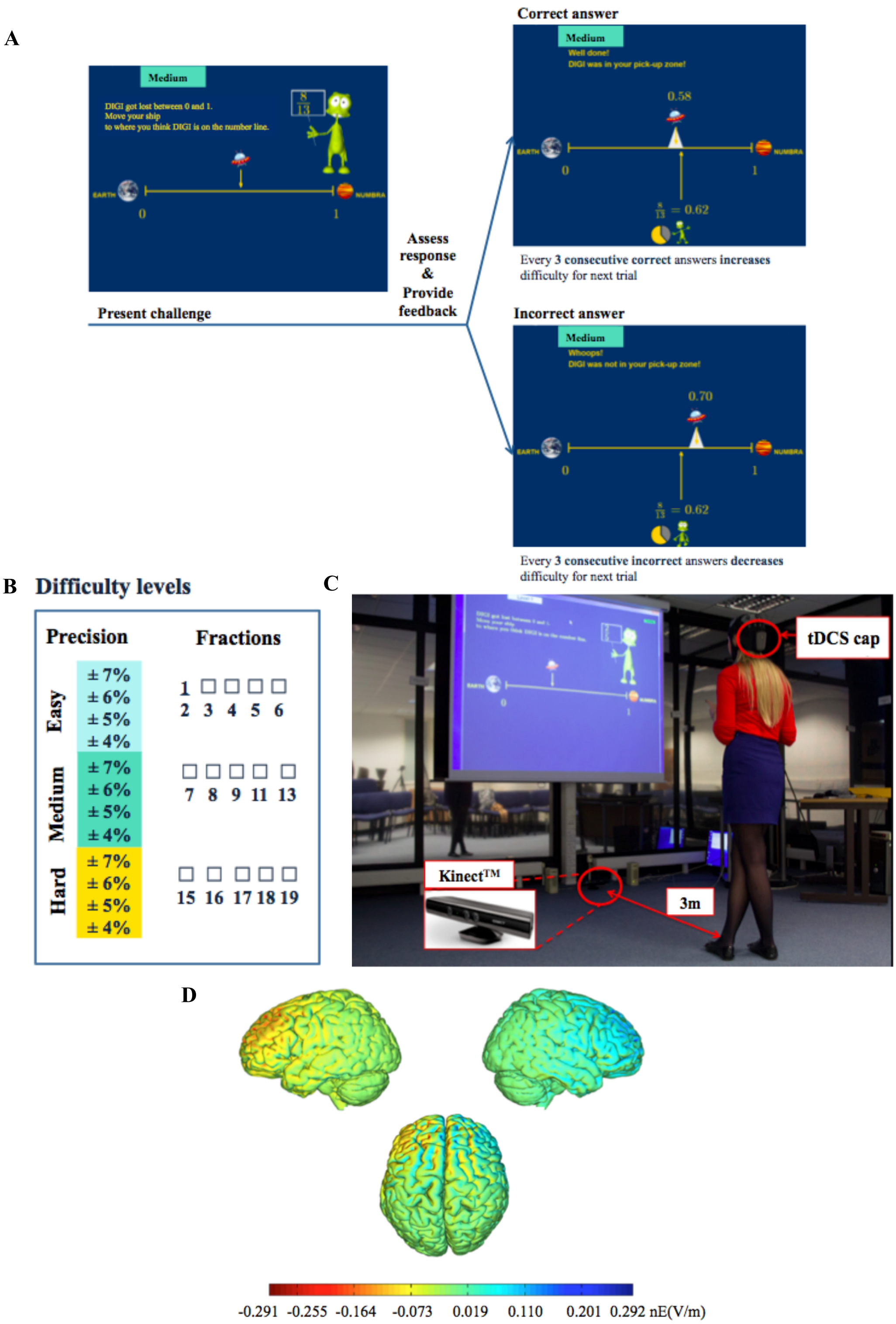

Figure 1 Combining brain stimulation with a numerical video game to enhance mathematical learning: A) Trial sequence, and design of an adaptive game. Feedback includes both concrete and abstract numerical representations to strengthen fractions understanding (Feenstra, Aleven, Rummel, & Taatgen, 2010). B) Fractions

attempted. Difficulty of each trial was systematically adjusted to participants' performance as a function of fraction category (Easy, Medium, Hard), and precision (allowed deviations from the target to be considered a correct response; ±7%, ±6%, ±5%, ±4% of the number line range). As such, participants were challenged to map fractions with greater accuracy at their maximal capacity. C) Experimental setup consisted of a numerical video game that involves body movements that are detected by a motion sensor, KINECT^{TM} and a wireless tDCS cap. To map fractions, participants moved their bodies from side-to-side to locate a spaceship on a virtual number line based on the fractions presented. The screen was 1.5x1.2 meters and was positioned 3 meters away from participants' standing position. D) Current field intensity map over the right-anodal (blue) and left-cathodal (red) dlPFC shown by computational simulation using the modelling engine of the NIC software (Neuroelectrics Inc.). Currents applied are maximally focused on the cortical surface near the perimeter of the electrodes, in the direction of the other electrode (Miranda, Lomarev, & Hallett, 2006; Miranda, Mekonnen, Salvador, & Ruffini, 2013).

Methods

Participants

Healthy, right-handed adults (n=30; 20 females, mean=24.2±2.1 years) with no history of neurological or psychiatric disorders provided their informed consent, and participated in this study. I assigned them into three groups, receiving either 1) active tDCS (n=10, 4 males, mean=24.6±3.8 years) throughout video game training; 2) sham tDCS (n=10, 2 males, mean=23.9±2.5 years) throughout video game training; or 3) active tDCS throughout non-mathematical visuospatial tasks, as an active control group (n=10, 4 males, mean age=24.1±2.0 years) later in the experiment. I matched participants across groups (sham and active tDCS) based on their performance on the standardized mathematics test (Wechsler Individual Achievement Test, Second UK Edition, WIAT-II UK). I received ethical approval from the Berkshire Research Committee to conduct this study, and the methods were carried out in accordance with approved guidelines.

Video game

Motivated by previous research that suggest embodiment during training promotes better training outcomes (Fischer et al., 2011; Link et al., 2013; Moeller et al., 2012), I designed an adaptive video game that involved participants to physically move their body from side-to-side to map fractions on a visually presented number line. Participants' movements were recorded by a time-of-flight camera, KINECT^{TM} (Figure 1C). For practice, participants performed four trials before their first training session. The game recorded the RTs and accuracy (deviation from target answer) of responses.

I conducted analyses up to Level 3 of this game, as 5 participants did not achieve beyond this level on Day 1. These Levels were categorized: Easy, Medium, and Hard based on their level of difficulty (Figure 1B) (For full stimulus list of the game, see Table 1). Each Level was subdivided into 4 levels of 'Precision', which represent the extent of deviation allowed from the target to be considered a correct response. The lowest precision represents ±7% allowed deviation from the target fraction based on the range of number line, while the highest precision represents ±4%, with two intermediate levels defined in steps of ±1%. I chose these specific levels of precision based on my pilot data on healthy adults; the easiest level (±7%) was the least demanding, but it was not effortless, while the most difficult level (±4%) was challenging, but not unreachable. The levels in between (±5%, ±6%) provided trials with gradual increase in difficulty to stretch the capacity of participants. In sum, the level of difficulty was represented by the category of fraction, and level of precision within that category. Each trial began with the presentation of a fraction challenge, followed by a response window, and an immediate assessment of a response with feedback (Figure 1A). A response was considered correct if the position mapped on the number line was within the allowed deviation from target fraction. Each participant started the game by mapping easy fractions with the lowest precision, ±7% from target. With every 3 consecutive correct responses, they were challenged by the requirement of a higher precision of mapping, i.e., ±6%, followed by ±5% and ±4%. With every 3 consecutive incorrect responses, participants were demoted by a category or precision level. This game is adaptive in nature, and automatically challenges participants to map fractions close to their maximal capacity. In sum, the level of difficulty was represented by the fraction category and level of precision within that category.

The fraction category was categorized by the size of fractions (Figure 1B), which increase from Easy to Hard, and therefore require increasingly precise mapping on the number line. Note that the more difficult, bigger fractions do not share the lowest common multiple with the easier fractions (see Table 1).

Level	Number line range (anchors)	Range of fractions numerators	Range of fractions denominators	Description
1	0-1	1-5	2-6	Simple fractions for all possible combinations
2	0-1	2-9	7-11	Simple fractions for all possible combinations
3	0-1	2-16	15-19	Simple fractions for all possible combinations
4	0-1	3-19	21-29	Two simple fractions each for denominators ranging from 21-29. Half of the numerators are even numbers.
5	3/32-1	5-32	31-41	Two simple fractions each for denominators ranging from 31-41. Half of the numerators are even numbers.
6	3/32-1	12-34	31-41	Two simple fractions each for denominators ranging from 31-41. Half of the numerators are even numbers. The initial anchor and the target needs to be converted to fractions with common denominators
7	5/48-39/42	1-19	3-45	All possible sets of fractions where

				both anchors and targets need to be converted to fractions with common denominators.

Table 1 List of fractions used in the numerical video game.

Transcranial direct current stimulation

For the active tDCS group, I applied 1mA tDCS to their bilateral dlPFCs (right, F3: anode, left, F4: cathode) for 30 minutes on 2 separate days (within 3 days) throughout the video game training. Stimulation was delivered by a wireless tDCS cap through two 25cm^2 circular sponge electrodes (Neuroelectrics Inc., Barcelona). Note that the current densities were not localised in one hemisphere (Figure 1D). Meanwhile, the sham group received identical video game training to the active group, but tDCS was applied for only 30 seconds (15 seconds ramp-up, 15 seconds ramp-down at the beginning and at the end of the training, respectively). Previous studies have shown that this brief stimulation triggered a sensation similar to the active tDCS, but assumed to produce negligible effects on the neuronal populations at the sites of stimulation (Fritsch et al., 2010; Gandiga et al., 2006). Finally, the active control group received tDCS following the same parameters as the active tDCS group, but during non-mathematical visuospatial tasks (Blocks Design subtest from the Wechsler Abbreviated Scale of Intelligence, WASI test).

Cognitive assessments

I conducted cognitive assessments before and immediately after training, as well as 2 months after training to assess transfer and long-term effects. I tested participants on their mathematical achievement and working memory capacity (verbal and visuospatial).

I tested their mathematical achievement using the Wechsler Individual Achievement Test 2nd UK Edition (WIAT-II, UK). This consists of the subset tests on Numerical Operations and Mathematical Reasoning. I used the composite scores to control for any differences in mathematical achievement during group allocation, and to assess the effect of individual differences on training outcomes for active and sham tDCS. I assessed verbal and visuospatial working memory (WM) capacities using Digit Span and Corsi blocks respectively (both forward and backward orders for each test).

Statistical Analyses

Response times and accuracy (absolute deviation of response from target) I analysed the RT and accuracy of training data up to Level 3 and within ±3 standard deviations (SD) of the mean using a 4-way mixed analyses of variance (ANOVAs). I used Time (Day 1, Day 2), Level (Easy, Medium, Hard fraction problems) and Precision (±7%, ±6%, ±5%, ±4% from the target answer based on the number line range) as the within-subject factors, and Group (tDCS, sham) as the between-subject factor. Two months later, I analysed data using a 3-way analysis of covariance (ANCOVA) with Category, Precision and Group. I included Day 1 RTs as a covariate to control for baseline performance, as it was correlated with training performance 2 months later (n=20, Pearson r=.72, p<.01; Spearman r=.84, p<.01).

Overall performance I took into account all levels in the game by conducting both Pearson and Spearman correlation analyses between overall levels (max=7 levels x 4 precision levels = 28 levels) and participants' baseline mathematical achievement. Note that I excluded one participant for being an outlier (>2.5 SD from the mean) and when I assessed the gain from training at the end of the game, I controlled performance on Day 1 as baseline performance as it was correlated with performance on Day 2. I controlled for Day 1 instead of subtracting it, as it is recommended as the best method given my study design; I allocated groups based on participants' performance at pre-test where their scores did not differ (Edwards, 2001; Van Breukelen, 2006).

Results

I began this experiment with 2 groups, active tDCS and sham tDCS during video game training. To further examine the role of the current video game, I conducted an additional experiment involving an active control group. I reported the results from this control experiment at the end of this section, as participants were not randomly assigned to this group in the same fashion as the active and sham tDCS groups. Participants' game performance was represented by RT and accuracy. Similarly, I assessed WM assessed using Digit Span and Corsi Blocks.

Short-term effects

Response times

I found that the more difficult the mapping requirement (precision) the longer participants took to map fractions [F(2,34)=32.23, *p*<.001, MSE=21.17, η^2_p =.66]. Of interest, I found an interaction between Time, Precision and Group [F(3,51)=4.02, *p*<.03, MSE=7.33, η^2_p=.45]. Through further analysis, I found that this interaction was due to a significant simple interaction between Precision and Group on the first day of training [F(3, 51)=5.23, MSE=3.833, *p*=.003, η^2_p=.24]. Post-hoc independent *t*-tests further showed that the precision of the game influenced the RT of the sham group on the first day; there was a higher RT in the most difficult precision (4%)

compared to other precision levels (p<.04). By contrast, I found that Precision did not affect RT in the active tDCS group [$F(3,27)=1.66$, $p=.2$, $\eta^2_p=.16$; mean RT difference between groups: $p>.2$]. The observation of longer RTs of the sham group in mapping fractions within 4% deviation from targets indicates that more mental resources might be required for more accurate spatial mapping on Day 1. I did not find effects of tDCS on Day 2 ($p>.4$) (See Figure 2).

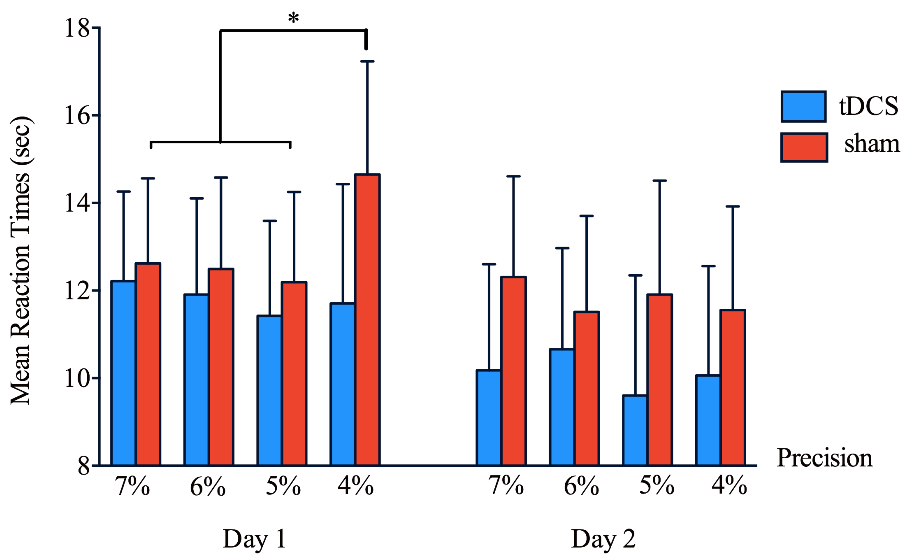

Figure 2 Three-way interaction between Time, Precision and group in mean RT of training on Day 1 and 2. This interaction stemmed from a significant two-way interaction between Precision and group for Day 1 (left panel) only. This was contributed by a significant difference within the sham group between the hardest precision, 4%, and 7% and 5%. Error bars represent one standard error of mean (SEM).

Accuracy

I found that performance on Day 2 was more accurate [Time: $F(1,17)=12.54$, $p=.003$, MSE<.001, $\eta^2_p=.43$]. Of interest, I found an interaction between Precision and Group [$F(3,51)=3.77$, $p=.02$, MSE<.001, $\eta^2_p=.18$]. While I did not find significant differences between groups in each precision levels (p>.19), I found that the simple main effect of Precision was significant for the sham group [$F(1,9)=17$, $p=.003$, $\eta^2_p=.65$]. Through linear trend analysis, I found that 70% of the variance in this interaction was associated with the sham group's decreased deviation from the correct location with increasing precision demands (linear trend analysis: $p<.001$) (Figure 3). On the contrary, I found no effects of precision demands on the accuracy of the tDCS group [$F(1,8)=.001$, $p>.98$, $\eta^2_p=.001$, linear trend analysis: $p>.58$] (Figure 3). Notably, I found a trend toward shorter RTs in the most demanding precision level (±4%), but with lower accuracy in the active tDCS group. I conducted further analysis, which suggested that this was not due to a speed-accuracy trade-off ($r=.02$, $p>.91$).

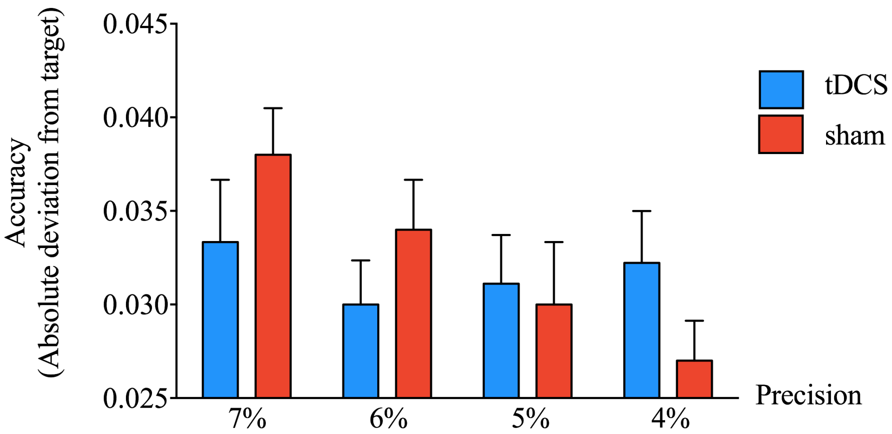

Figure 3 Accuracy as a function of Precision and Group. Note the linear trend in the decreased deviation in the sham group. Group differences in accuracy at 4% precision were not significant ($t(18)=1.35$, $p=.19$). Data represent mean ± one SEM.

Number of trials

On average, participants attempted the following number of trials on Day1: 102 ± SD=26, Day 2: 101 ± SD=28, and 2 months later: 104 ± SD=23. I conducted a 4-way ANOVA with Time (Day 1, Day 2) x Level (3) x Precision (4) x Group (active, sham tDCS) on the number of trials up to Level 3, as 4 participants did not perform beyond this level. I did not find any significant interactions with Group, all p>.8. I found main effects of Day [$F(1,17)=6.49$, $p=.021$, $n^2_p=.28$] and Precision [$F(3,51)=13.0$, p<001, n^2_p =.43].

The influence of individual differences

As hypothesized, I found that training effects were modulated by individual baseline mathematical achievement (Figure 4A). Specifically, within the sham group, those with higher baseline mathematics achievement progressed through more levels during training ($r=.77$, $p<.01$). This pattern is in line with those of a typical classroom, whereby those who started with higher baseline abilities tend to have higher achievements (Duncan et al., 2007). This pattern has also been found by previous cognitive training studies (Bissig & Lustig, 2007; Link et al., 2013; Lövdén et al., 2012). Of interest, I found an opposite pattern in the tDCS group; those with lower baseline mathematical achievement progressed through more levels during training ($r=-.76$, $p<.01$). I found that group correlations differed significantly (Steiger's Z-test, $Z=3.62$, $p=.002$)(J. Cohen & Cohen, 1983). Using Spearman correlations, I found similar results [sham: $r=.57$, $p<.08$; tDCS: $r=-.72$, $p<.02$] (Figure 4B). Note that 'ceiling effects' could not explain the current observations, as both sham and active tDCS groups achieved on average, similar levels at the end of training (p>.32). The explanation of 'regression to the mean' is also unsatisfactory, as it does not explain the differences in the slopes between groups (Barnett, van der Pols, & Dobson, 2005).

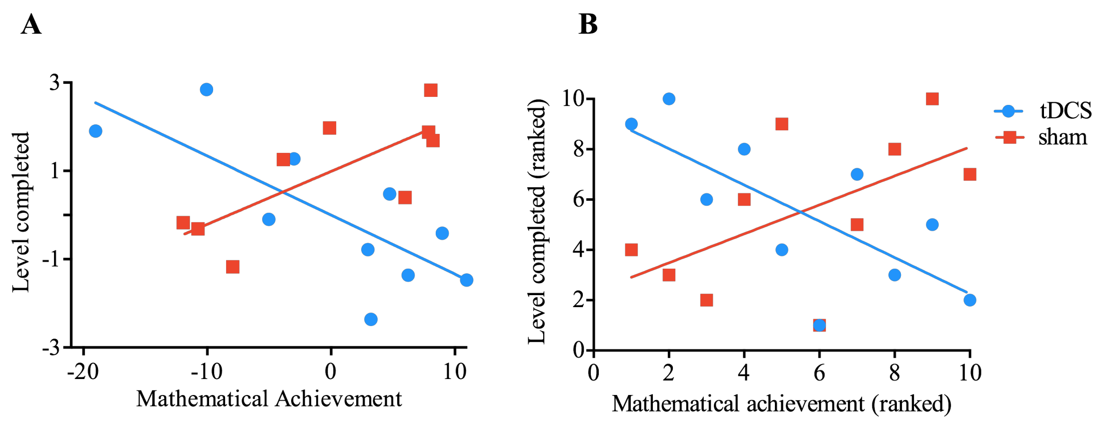

Figure 4 Double dissociation in the outcomes of tDCS in combination with video game training vs. video game training alone: combined tDCS and training is more beneficial for individuals with lower baseline mathematical abilities, while training alone is more beneficial for those with higher baselines. A) Pearson and B) Spearman correlational analyses demonstrate the modulatory effects of baseline mathematics achievement and levels completed at the end of training. Data in panel A represent residuals after partialling out the correlation with performance on the first day of training. Note that one participant from the sham group was excluded for underperforming by 2.5 SD from the mean. Note that some data points on panel B overlapped, resulting in the appearance of less points.

Working memory

I conducted a 4-way ANOVA with Task (verbal WM, visuospatial WM), Order of retrieval (forward, backward) and Time (pre-training, post-training) as within-subject factors, with Group (tDCS, sham) as the between-subject factor. I found an interaction between the Task (verbal, visuospatial), Time, and Group [$F(1,18)=22.4$, $p<.0001$, MSE=.91, $\eta^2_p=.56$]. Note that this interaction was not contributed by the Order of retrieval (forward vs. backward) ($p>.38$). Therefore, I did not decompose this interaction into backward and forward to avoid type I error. Nonetheless, I presented the interaction of Time and Group for verbal WM separately for backward and forward spans, which shows a similar pattern (see Figure 5). I decomposed the 3-way interaction between Task, Time and Group by verbal and visuospatial WM.

Verbal WM I found an interaction between Time and group [$F(1,18)=10.62$, $p<.004$, MSE=1.14 $\eta^2_p=.37$] (Figure 6A). Notably, while the active tDCS and sham groups did not differ in capacity at pre-test [$t(18)=.37$, $p>.72$], active tDCS group showed improved verbal WM capacity compared to the sham group at post-test [$t(18)=3.46$, $p>.002$, Cohen's d=.63]. I found that this improvement was only shown by the tDCS group [tDCS: $t(9)=3.09$, $p<.01$, Cohen's d=.72], as the sham group did not show any changes in capacity. Note that the decline shown by the sham group is not significant: $t(9)=.8$, $p>.44$.

Visuospatial WM I did not find any significant changes in the simple main effects, and interaction between Time and Group [all $F<.2.42$, $p>.14$] (Figure 6C).

Long-term effects (2 months post-training)

Response times

At follow-up, I ran a 3-way ANCOVA with Level, Precision and Group on RT two months post-training. I found that the tDCS group was 2.4 seconds (20%) quicker than the sham group fractions mapping [Group: $F(1,17)=4.84$, $p<.04$, MSE=.001 $\eta^2_p=.22$] (Table 2). I found a significant linear trend in the RT across Time (Day 1, Day 2, 2 months later), [$F(1,18)=10.29$, $p=.005$, $n^2_p=.36$], although the interaction with Group was only a trend, [$F(1,18)=3.12$, $p=.094$ $n^2_p=.15$]. Through further analyses on separate Groups, I found a significant linear trend in the tDCS group, [$F(1,9)=8.74$, $p<.032$, $n^2_p=.49$, having corrected for multiple comparisons, due to non-significant interaction], but not in the sham group [$F(1,18)=1.78$, $p>.43$ $n^2_p=.17$].

Accuracy

I found a significant interaction between Precision and Group [$F(3,48)=6.28$, $MSE<.001$, $p<.001$, $\eta^2_p=.28$] with Day 1 as a control. This stemmed from more precise fractions mapping of the active tDCS group than the sham group in the easiest precision level [±7%; $t(18)=2.71$, $p<.01$, Cohen's $d=.54$] (For accuracy values, see Table 2).

Number of trials

I found that when the follow-up data was included, the interaction between Precision and Group was significant [$F(3,51)=17.21$, $p=.035$, $MSE=5.58$, $n^2_p=.15$], although I did not find significant differences between Groups in all Precision levels (all $p>1.5$) when decomposing this interaction.

Working memory

I found that the transfer effect to verbal WM in the active tDCS group was sustained after 2 months [$t(18)=3.45$, $p<.002$, Cohen's $d=.63$] (Figure 6B), and there was no effect on visuospatial WM capacity [$t(18)=.13$, $p=.89$] (Figure 6D). These findings are consistent with those immediately after training, indicating that the type of WM transfer effects is dependent on Group [$F(1,18)=6.13$, $p<.02$, $MSE=6.06$, $\eta^2_p=.44$].

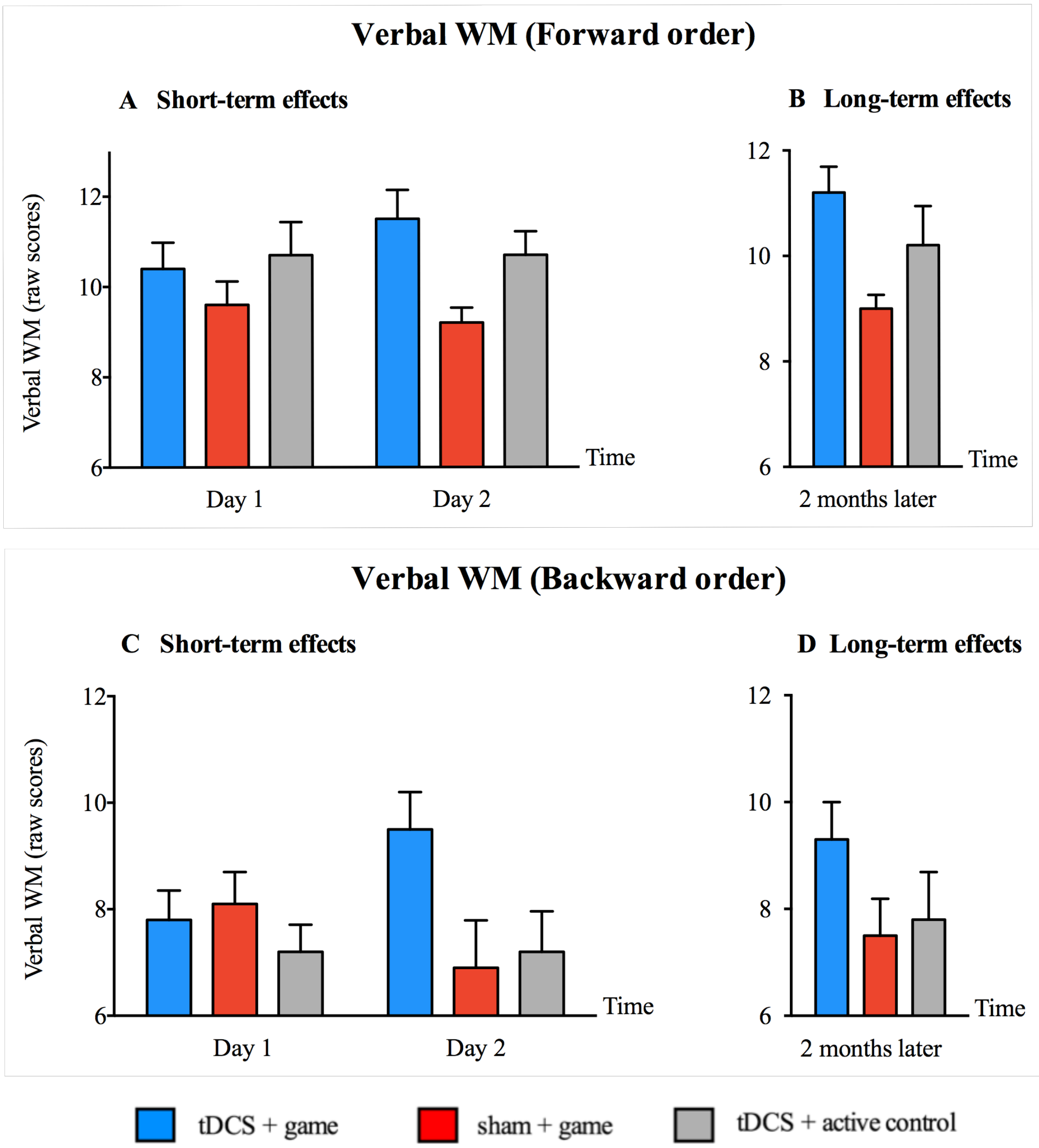

Figure 5 Verbal WM forward and backward. Data are shown as mean ± one SEM.

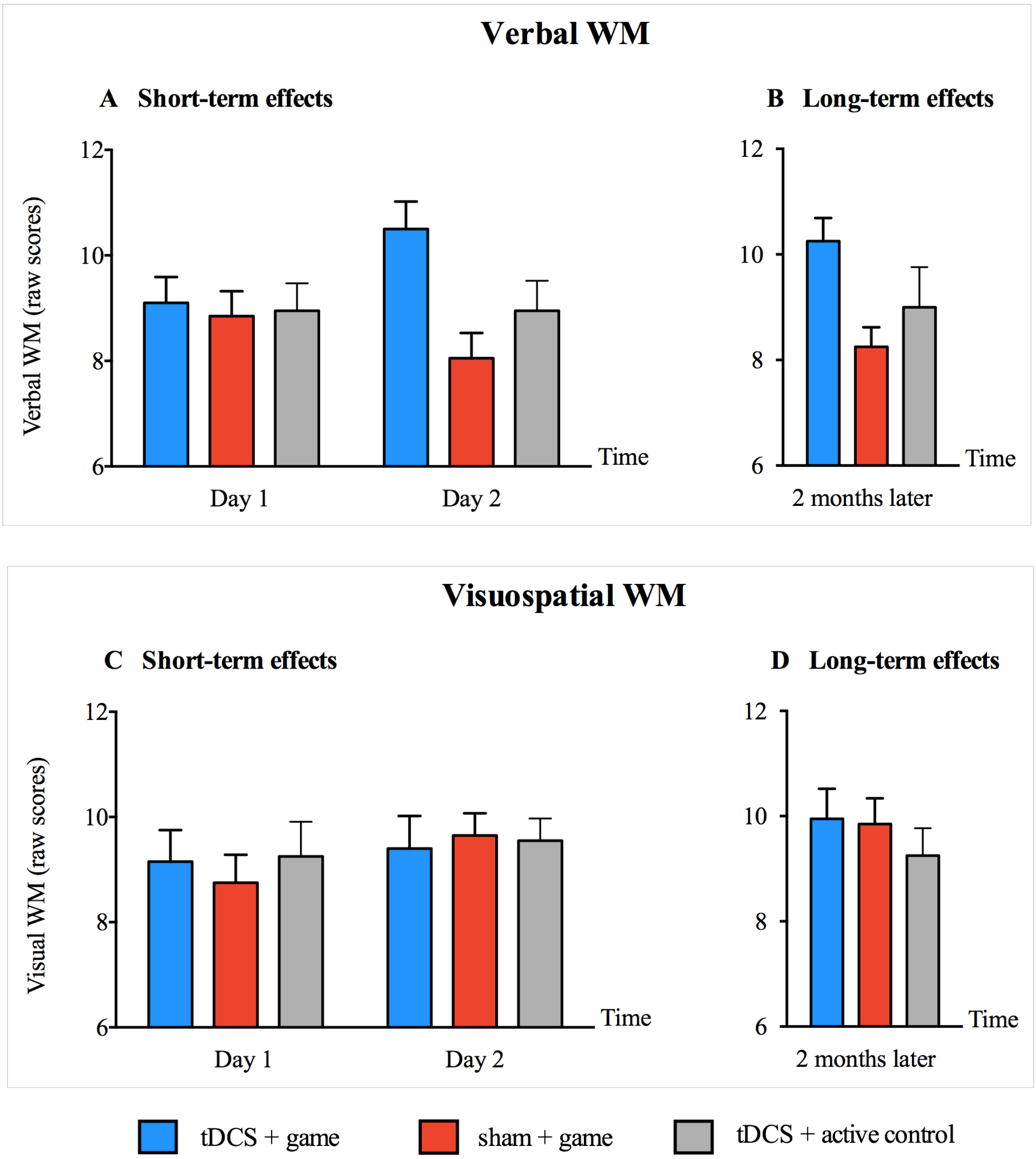

Figure 6 Transfer of training gains from numerical video gaming combined with tDCS. A) Only the active tDCS group showed increased verbal WM capacity immediately after training, and B) 2 months later. C) No improvements were found in the visuospatial WM capacity of participants immediately after training or D) 2 months later. Data are shows mean ± SEM.

The role of training in tDCS effect

In order to investigate whether the combined method of tDCS and the video game is the critical factor to WM effects and not a general effect of tDCS on dlPFC *per se*, I conducted a separate experiment. Specifically, I recruited an active control group (n=10; matched by age and baseline mathematical achievement) who trained on Matrix Reasoning and Block Design (subtests of the Wechsler Abbreviated Scale of Intelligence, WASI) while receiving active tDCS. Both tasks required visuospatial skills but non-mathematical skills. However, due to the nature of these tasks, I could not directly and accurately compare their difficulty levels. I measured performance on both tasks using raw and scale scores. I recorded participants' RT and the tasks took about 30 minutes in total. The idea was that these tasks served as "placebo training", i.e., not the main training, but engage visuospatial processing, a similar feature to our game. Through this active control group, I could (1) disentangle the training effects specific to the current video game; (2) control to some degree, the cognitive processes engaged during periods of receiving active tDCS (Gruberger, Ben-Simon, Levkovitz, Zangen, & Hendler, 2011; Jolles & Crone, 2012). The key role of this active control group was to compare the verbal and visuospatial WM effects with those of the active and sham tDCS groups. As the active control group did not train on the video game, I did not have any accuracy or RTs on the game for this group. When I included the results from this active control group to the ANOVA, Task (verbal, visuospatial) x Time (Day 1, Day 2) x Group (active tDCS, sham tDCS, active control), I found that the interaction between the Task, Time and Group remained significant [$F(1,28)=15.41$, $p=.012$, $MSE=2.06$, $n^2_p=.21$] (Figure 6). I then decomposed the interaction based on the WM tasks (as in previous section on WM).

Verbal WM I found that the interaction between Time and Group was significant [$F(2, 28)=7.89$, $p=.009$, $MSE=2.72$ $n^2_p=.22$]. The active tDCS and control groups (both sham and the active control groups) differed in verbal WM at post-testing [$t(28)=3.07$, $p=.005$]. Of interest, only the active tDCS group showed improved WM capacity at post-testing [tDCS: $t(9)=-3.1$, $p<.01$; control groups: $t(19)=1.02$, $p=.32$].

Visuospatial WM I did not find a significant interaction between Time and Group ($p>.59$, $n^2_p=.01$).

RT (Raw values)			
	Day 1	Day 2	2 months later
tDCS	11.81 (4.27)	10.79 (3.43)	9.63 (2.91)
Sham	12.99 (3.45)	11.82 (4.85)	12.07 (4.02)
Improvement *within* groups (%)			
Time	Day 2 vs. Day 1	2 months later vs. Day 2	2 months later vs. Day 1
tDCS	8.6	10.8	18.5
sham	9	-2.1	7
Difference *between* groups (tDCS-sham, %)			
Time	Day 1	Day 2	2 months later
	1.7	8.7	20.3
Accuracy (Raw Values)			
	Day 1	Day 2	2 months later
tDCS	0.0327 (.0071)	0.0287 (.0072)	0.0271 (.0081)
Sham	0.0343 (.0093)	0.0287 (.0054)	0.03000 (.0059)
Improvement *within* groups (%)			
Time	Day 2 vs. Day 1	2 months later vs. Day 2	2 months later vs. Day 1
tDCS	12.2	5.6	17.1
sham	16.3	4.5	12.5
Difference *between* groups (tDCS-sham, %)			
Time	Day 1	Day 2	2 months later
	0.5	0	0.1

Table 2 Game RT and accuracy values on improvements within and between groups. Improvements within and between groups (tDCS vs. sham) are represented by % changes. Data shows mean ± SD.

Discussion

In the current study, I examined whether combining tDCS and an engaging video gaming would 1) further improve training outcomes compared to training alone with long-term effects; 2) induce transfer to beyond trained domain; and 3) produce training outcomes that are modulated by individual differences in baseline mathematical abilities.

As predicted, tDCS further improved training performance, with immediate and long-term gains compared to training alone. This improved performance is more pronounced between the two groups with increasing difficulty levels; while the sham group showed a decline in performance with higher precision requirement (accuracy, RT), this was not the case for those who received active tDCS. This finding supports a recent finding that showed tES mitigated task difficulty (Popescu et al., 2016). One potential explanation for this observation is that tDCS might have allowed more mental resources to engage effectively with more challenging tasks (Pope & Miall, 2012). Notably, after only two days of 30-minute training, the active tDCS group were on average 13% quicker in mapping fractions, and continued to improve by another 8% when tested 2 months later without further training and use of tDCS (linear trend analysis: tDCS, $p<.02$; sham, $p>.2$, see also Results, and Table 2). It is worth highlighting that the delayed benefits mirrored those of a previous study that found improvements in memory only after 1 week after training (Floel et al., 2012).

This observation is also consistent with another finding that showed anodal tDCS during training induced positive offline gains compared to sham (Reis et al., 2009). Such gains were thought to result from enhanced protein synthesis following anodal tDCS during training, or the activation of the downstream interactions of learning-related protein synthesis by tDCS-induced excitability during and after training (Reis et al., 2009). Indeed, when training performance was assessed 2 months later without tDCS, the active tDCS group showed on average, a 20% faster response than their initial performance, while the sham tDCS group showed only 8% improvement (Table 2). Together, these findings suggest that 2 days of 30-minute training each, while receiving tDCS could have long-lasting impact on neuroplasticity. Further studies are needed to collect physiological data for the investigation of the underlying mechanisms.

On the subject of transfer, I found improvements in WM capacity, a domain that was not directly trained. Specifically, participants from the tDCS group recalled at least one item more than those from the sham and active control groups immediately after training, and 2 months later without further training and tDCS. This finding could offer practical implications, given the brevity of training and its transfer effects at the capacity level. Such level of effect has been previously demonstrated by training that took up to 100 hours of training (Schmiedek, Lövdén, & Lindenberger, 2010). Of importance, this transfer effect is exclusive to the combination of tDCS and the current video game training. I did not find any transfer effect form the sham or the active control group that trained on non-mathematical visuospatial tasks. These findings suggest that the mechanisms underlying these observations are not due to tDCS *per se*, but from the synergistic effects between tDCS and the current video game. This specific transfer effect to verbal WM might indicate the predominant use of the verbal component as a strategy during our game. Indeed, to map fractions as precisely as possible on the number line, participants had to retain symbolic fractions in mind. Furthermore, fractions problem solving and mathematical computation have been linked to verbal WM (Fuchs et al., 2014; K. M. Wilson & Swanson, 2001). Another potential explanation is that since digit span forward and backward engage overlapping functional neural system linked with WM, specifically the right dlPFC (Gerton et al., 2004), anodal tDCS over the right dlPFC during video game training might have strengthen the synaptic efficiency between dlPFC and overlapping networks, as suggested by previous tES and neuroimaging research (Dahlin et al., 2008; Reis et al., 2014; Reis et al., 2009). Further studies are need to examine whether this effect is contributed by enhanced protein synthesis during training, previously suggested to induce downstream interactions of learning-related proteins during motor learning (Reis et al., 2014). Currently, it is difficult to explain the lack of improvement of the active control group. Research is needed to examine how factors such as training, and stimulation montage could have affected such outcomes. Nonetheless, this null finding is independent from the conclusions of current findings.

Finally, I found that the effects of the combined approach of tDCS and video game training and training alone were modulated differently by individual baseline in mathematical abilities. Specifically, there was an opposite pattern in the relationship between training performance and baseline achievement between the sham and tDCS group. I found that within the sham group, those with higher baseline achievement progressed through more levels in the game, consistent with the common observation of "those who start ahead, stay ahead" in a typical classroom (Duncan et al., 2007) and findings of previous cognitive training studies (Lövdén et al., 2012). By contrast, I found that those with lower baseline achievement progressed through more levels in the game in the tDCS group. These findings support and expand on previous findings that showed tDCS efficacy is modulated by baseline performance in a categorical manner; for example, low vs. high mathematics anxiety (Sarkar et al., 2014), low vs. high visual short-term memory (Tseng et al., 2012) and trained vs. untrained musicians (Furuya et al., 2014). Furthermore, the current observation is in line with the prediction that those with lower baseline abilities would achieve higher gains through modulation of cortical excitation and inhibition using methods such as tDCS (Krause et al., 2013). A potential explanation is that the effects of tDCS are more pronounced for difficult trials as performance on easy trials are likely to be nearer to the optimal response, and tDCS effects are less likely to produce further, significant behavioural improvements (Bonaiuto & Bestmann, 2015). Therefore, it is plausible that participants with lower baseline achievement, who were more likely to have found the training more difficult than those with higher baseline achievement, benefited more from tDCS. The limited benefits associated with tDCS amongst participants with higher baseline achievement could also be influenced by individual limits in cortical excitability [(H. I. Kuo et al., 2013; Sarkar, Dowker, & Cohen Kadosh, 2014; Tseng et al., 2012), for review see, (Krause et al., 2013)]. As the physiological effects of tDCS on human cognition are likely to be complex, further studies that account for the complex biological systems are needed to understand the mechanisms underlying these observations (Bonaiuto & Bestmann, 2015).

Together, current findings suggest that when assessing the efficacy of tES, it is important to consider the influence of inter-subject variation in baseline cognitive achievement. This could be particularly relevant for stimulation over regions that are more strongly influenced by genetic factors such as the dlPFCs (Kanai & Rees, 2011; Thompson et al., 2001). Modelling of the interactions between tES and individual neural profiles could refine our understanding on the mechanisms of tES. Furthermore, current findings demonstrate the potential of tDCS for reducing, instead of increasing pre-existing disparities in performance. This addresses concerns about the potential risk of tES for widening the cognitive gap across healthy individuals (Cohen Kadosh et al., 2012; Riggall et al., 2015). Further work is needed to examine how individual differences and tDCS would interact within other cognitive domains and populations.

Despite comparable sample size to the literature on cognitive studies using tES (Krause & Cohen Kadosh, 2013), the current study could have benefited from a larger sample. Nonetheless, the current modest sample had sufficient power to detect group difference and interactions (Friston, 2012), and found effect sizes that comparable to those reported by cognitive studies using tDCS [for a review, see (Jacobson et al., 2012)]. Current findings could serve as motivation to conduct studies with larger samples, which also examine the underlying neural mechanisms. Further work is also needed to disentangle whether the training improvements were due to arithmetic or visuospatial accuracy. It was difficult to disentangle these two cognitive components, which are interlinked and involved in numerical mapping, given the nature the current video game. The addition of a control task that could tease apart the contribution of each component is ideal for this purpose.

In sum, I found that short- and long-term improvement of cognitive functions is achievable within the timescale of an hour. Conceptually, the current findings indicate that the combination of tES and a training with improved ecological validity could produce synergistic effects that are more potent than those achieved by training alone.

Furthermore, these findings offer practical implications, as the current combined approach of non-pharmacological methods required minimal time investment. Understanding the inter-individual variations in the outcomes and response to tES and training could delineate the mechanisms underlying such interactions, and efficacy of these enhancement methods for different individuals, which could advance the development of personalised cognitive enhancement.

Chapter 3

Improving learning and cognition of the atypically developing brain using a numerical video game and transcranial random noise stimulation

Abstract

Learning disabilities that negatively impact on individual life and socioeconomic outcomes (DSM-V, ICD-10) are linked with atypical neurodevelopment, and mainly treated with behavioural interventions. Most of existing interventions are time-consuming, and few have shown efficacy that are supported by empirical evidence. Transcranial random noise stimulation (tRNS) is a form of painless tES that has been shown to improve learning in healthy adults. Its potential for remediating neural atypicalities of developing brains, which are linked to a greater degree of neuroplasticity has been proposed and debated, but not empirically tested. I investigated the potential of tRNS and a video game on number line mapping that involved bodily movements for improving learning of children with mathematical learning disabilities (MLD) at a school for special learning needs. Compared to sham tRNS, I found that children with MLD showed a steeper learning curve and improved response accuracy during training. Independent of tRNS, training outcomes correlated positively with scores on a standardized diagnostic mathematical test, suggesting that training gains were generalizable and meaningful in the classroom. Overall, my study contributes a ‘proof-of-concept’ for using tRNS during cognitive training to improve learning and cognition of children with learning disabilities.

Introduction

Learning disabilities due to atypical neurodevelopment negatively affect the life outcomes of up to 10% of the population, or 2 to 3 pupils in every classroom (Beddington, Cooper, Field, Goswami, Huppert, Jenkins, Jones, et al., 2008; Butterworth & Kovas, 2013; Stein, Blum, & Barbaresi, 2011). Most interventions involve a significant investment of time and effort, but have shown improvements that rarely generalize beyond trained materials (Geary, 2011). Furthermore, few have shown efficacy that are supported by empirical evidence (Kroeger, Brown, & O'Brien, 2012; Rabipour & Raz, 2012).

Transcranial random noise stimulation (tRNS) is a form of tES that delivers random noise oscillations to selected brain regions, thought to modulate underlying cortical excitability (Terney et al., 2008). Its application on adult population within recommended guidelines has been considered safe and painless (Fertonani, Ferrari, & Miniussi, 2015a). TRNS has been proposed to increase neuronal excitability via principles of stochastic resonance, whereby weak neural signal detection in the central nervous system is enhanced when ‘noise’ is added (Miniussi et al., 2010; van der Groen & Wenderoth, 2016). While tRNS during cognitive training has been shown to promote better learning of healthy adults within days, with lasting effects up to 6 months (Snowball et al., 2013), the significance of such effects in the real-world (i.e., training and transfer effects on everyday tasks in non-laboratory settings) remains to be examined. Specifically, its potential for remediating neural atypicalities of developing brains that are associated with a greater extent of neuroplasticity (Johnston, 2009) has been proposed (Krause & Cohen Kadosh, 2013) and discussed (Davis, 2014), but not empirically tested.

In the current study, I investigated the effects of tRNS during cognitive training on the learning of children with MLD compared to cognitive training alone. I focused on MLD, as this condition is under-researched compared to other learning disabilities of similar prevalence and socioeconomic impact such as dyslexia (Beddington, Cooper, Field, Goswami, Huppert, Jenkins, Hannah, et al., 2008). I used tRNS, as studies have consistently shown that it supports steeper learning and better training outcomes within the numerical domain in healthy adults compared to training alone (Cappelletti et al., 2013; Cappelletti et al., 2015; Popescu et al., 2016; Snowball et al., 2013). Of particular relevance, tRNS effects were found to be more pronounced with increased arithmetic difficulty (Popescu et al., 2016), a condition akin to the daily challenges of children with MLD. I applied tRNS over children's bilateral dlPFCs (F3 and F4 based on the International 10-20 system mapped on a wireless cap, Figure 1A), shown to be engaged in mathematical learning as evidenced by neuroimaging (Zamarian et al., 2009) and tRNS studies on healthy adults (Popescu et al., 2016; Snowball et al., 2013).

To examine the relevance of tRNS effects to the real-world, I ran this study in a school specialized for learning disabilities. I conducted cognitive training using a video game that I designed [a professionally gamified version of the previous game in Chapter 2 to improve the ecological validity of training (Moreau & Conway, 2014)], and transfer tasks that reflect real-world learning (mathematics diagnostic test used by the school). Children were diagnosed by their school as having MLD on the basis of persistent underachievement of at least two levels below the age-expected National Curriculum levels. During training, children moved their body from side-to-side to map the location of a given number on a virtual number line, and registered their responses by raising both of their hands (Figure 1A). This feature of body movement is based on previous studies that showed embodiment in training promotes better training outcomes than those without (Fischer et al., 2011; Link et al., 2013; Moeller et al., 2012). My game featured number line mapping, which is a key predictor of mathematical achievement (Siegler & Booth, 2004). The level of difficulty of number line mapping was automatically adjusted to children's individual performance. Children were given feedback on their responses in each trial (Figure 1B). Based on a range of control measures (Table 1), children were pseudo-randomly assigned to receive either active or sham tRNS during training. I measured children's performance during training, and on cognitive tasks [Mathematical Assessment for Learning and Teaching, (MALT) and working memory (WM)] before and after training. I also recorded their experiences of tRNS using a questionnaire at the end of the study. Based on previous findings on young healthy adults (Cappelletti et al., 2013; Popescu et al., 2016; Snowball et al., 2013), I hypothesized that compared to training alone, tRNS during video game training would (1) improve the learning of children with MLD, and (2) promote transfer effects to a real-life task.

Methods and materials

Participants

Twelve children with MLD aged 8.5-10.9 (mean ± one standard error of the mean: 113.8±7.3 months) without other neurological or psychiatric illness participated in this study. I selected children from the same school, which was the only school that participated in our research at the time given the lack of safety records of tRNS for paediatric use. Children were diagnosed as having specific MLD by Fairley House

School (London), a specialised school for children with specific learning needs. I conducted children's training in the same room to control for any variance due to different learning environments. I pseudo-randomly assigned them into sham and active tRNS groups (Table 1). To participate in the current study, parents/guardians gave their written consent, and children gave their assent. I received ethical approval from the National Research Ethics Service Committee South Central-Hampshire B (11/SC/0401) to run the current study.

Controlled variable	**Active tRNS**	**Sham tRNS**	**Group differences**
Age (months) Mean (SD)	114.8 (6.6)	112.8 (8.5)	$t(10)=.46$, $p>.66$
Gender	5 boys, 1 girl	5 boys, 1 girl	$\chi^2(1)=0$, $p=1$
Mathematical performance Mean (SD)	13.5 (8.2)	13.2 (5.5)	$t(10)=.08$ $p>.94$
Equivalent Mathematical Age (SD)	87.8 (15.2)	88.8 (10.6)	$t(10)=-.13$, $p>.9$
Working memory Mean (SD)			
Verbal			
Forward	4.67 (.52)	4.17 (.98)	$t(10)=1.1$, $p>.3$
Backward	2.67 (.81)	2.5 (.55)	$t(10)=.41$, $p>.69$
Visuospatial			
Forward	4.17 (.98)	3.83 (1.33)	$t(10)=.49$, $p>.63$
Backward	3.0 (.63)	3.0 (.89)	$t(10)=0$, $p=1$
Guessed condition	6/6 real	6/6 real	$\chi^2(1)=0$, $p=1$

Table 1 Children with MLD were matched across groups (sham vs. tRNS) based on their age, gender, mathematical abilities, and working memory capacity. Please note

that MALT provides the mathematical age equivalence based on raw scores but it does not provide a standardise score below a certain level of performance. Therefore, I presented the raw scores and the mathematical age equivalence. WM capacity is represented by standard scores.

Video game training

My video game training featured mapping numbers on a virtual number line that is approximately 1m on the interactive whiteboard. To map numbers projected on the screen, children physically moved their bodies from side-to-side. To register their responses (taken into account up to 2 decimal points for statistical analyses), they raised both hands in front of a time-of-flight camera (Kinect^{TM}; Figure 1A). Children mapped numbers of a range of difficulty levels, which was defined by the (1) range of number line; 0-5, 0-10, 0-50, 0-100, 0-500, 0-1000, and 0-1500, and (2) a range of precision levels (7%, 6%, 5% and 4% allowed deviation from the correct answer) within each difficulty level. Three consecutive correct answers increased the difficult level/precision level of the next trial, while three consecutive incorrect answers decreased the level/precision level difficulty of the next trial (Figure 1B). My game yielded three key measures: accuracy (precision of number mapping), response times (RT) and the level of each trial attempted. There were a total of 28 levels, consisted of 7 difficulty levels and 4 precision levels within each difficulty level. Children trained on this game for 9 days, 20 minutes each at school for 2 days per week.

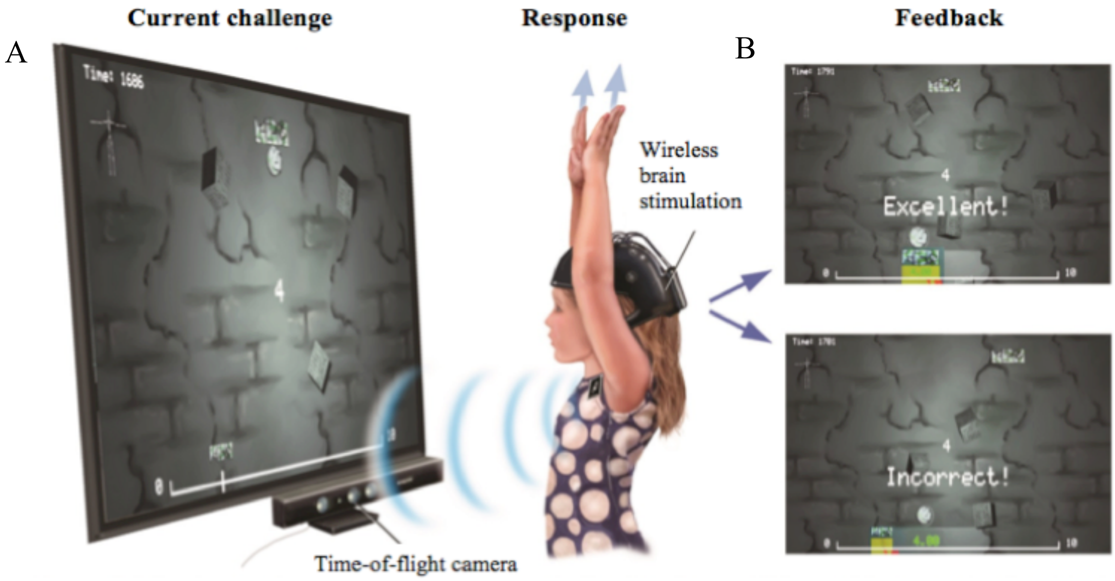

Figure 1 Transcranial random noise stimulation during video game training to improve learning of children with mathematical learning difficulties A) A child moved from side-to-side to map a number on a virtual number line while receiving wireless tRNS. Response for each trial was registered when both hands were raised. Body movements were detected by a time-of-flight camera, Kinect™. B) Examples of feedback for correct and incorrect responses. The game difficulty was automatically adapted based on individual performance; every 3 consecutive correct answers promoted the following trial to a more difficult level and vice versa.

Transcranial random noise stimulation (tRNS)

Children in the active tRNS group received 0.75mA to their bilateral dorsolateral prefrontal cortices (dlPFCs; F3, F4) delivered through two saline-soaked, 25 cm^2 circular sponges attached to a wireless tRNS cap that followed the International 10-20 EEG system (Neuroelectrics Inc., Barcelona). Children received tRNS for 20 minutes, throughout each training session.

I applied a lower dosage [75% of that typically administered to adults, (Ambrus et al., 2010; Cappelletti et al., 2013; Snowball et al., 2013)] having considered parameters that would influence current distribution and density at the site of stimulation such as thinner scalp, less cerebrospinal fluid, and smaller head size of the paediatric population (Kessler et al., 2013; Opitz, Paulus, Will, Antunes, & Thielscher, 2015). As a cautious approach, I ensured that there was at least one day between days of stimulation to minimize any potential cumulative side effects of tRNS on paediatric population (Davis, 2014) despite potentially stronger results with stimulation on consecutive days, shown by a previous tDCS study on adults (Alonzo, Brassil, Taylor, Martin, & Loo, 2012). Children in the sham group did not receive any tRNS. Nonetheless, they wore the wireless cap to control for any associated placebo effects. Children were blinded to their stimulation condition.

Working memory

Having considered the relationship between mathematical achievement and WM (Raghubar, Barnes, & Hecht, 2010) and my previous study [see Chapter 2, (Looi et al., 2016)], I assessed children's verbal and visuospatial WM capacity using Digit Span and Corsi Blocks, respectively. I also examined performance on these measures to monitor for any changes associated with training effects, as well as any potential cognitive side effects linked with stimulation (Brem et al., 2014; Iuculano & Cohen Kadosh, 2013). In the Digit Span task, I read aloud a series of digits and asked children to verbally repeat the sequence. The first trial consisted 2 digits, and with every 2 trials, the span increased by one digit. In the Corsi Blocks task, I tapped a sequence on a series of blocks, and asked children to repeat the tapped sequence. Similar to the Digit Span task, the first sequence consisted of 2 blocks, and with every 2 trials, the tap sequence increased by one block. I terminated each task when children provided 2 consecutive incorrect responses. I recorded the standard score of each task, which was represented by the maximum number of items recalled in 2 consecutive spans.

Mathematical assessment

I assessed children's mathematical performance using MALT, a standardized diagnostic test that is calibrated to the UK National Curriculum levels (Hodder Education UK, 2004). MALT is a common assessment tool used by schools to evaluate the mathematical performance of their students. I instructed children to solve as many mathematical problems as they could using pencil and paper within 45 minutes. I administered MALT before and immediately after the 9 days of training.

Statistical analysis

I used IBM SPSS Statistics to perform all statistical analyses, with the threshold for significance set at $p<.05$. I analysed video game RTs, accuracy, levels completed, and working memory data by running Analysis of Variance (ANOVA). To examine how Group (tRNS vs. sham) affected the transfer from training to mathematics performance, I ran a regression analysis. The analysis was performed using Amos 22 (Arbuckle, 2013) using the maximum likelihood estimator[3].

Video game Number ranges increased as a function of Levels (e.g., Level 1: 0-5, Level 2: 0-10, Level 3: 0-50 etc.). I standardised accuracy responses across all Levels [Absolute deviation from Target/Number range*100] to allow for comparison across

[3] This analysis was guided by Dr. Simon Lolliot from the Department of Experimental Psychology, University of Oxford, who is also a co-author on the manuscript of this study.

Levels, in line with previous studies (Siegler & Booth, 2004). I log-transformed (natural log) these scores, as they were positively skewed.

Transfer effects I used the normalised absolute percentage error as specified by the equation in the previous paragraph as a measure of the accuracy of training performance. I calculated the training gain in accuracy over the 9 sessions for each subject according to the following equation: [(Day 9–Day 1)/Day 1] and correlated it with children's improvement in MALT using the following equation: [(Post-training score – Pre-training score)/Pre-training score]*100.

Questionnaire on children's perception of tRNS

After the 9th training session, I asked children the following questions using a questionnaire:

1. Did you receive brain stimulation? (A. During all sessions; B. Sometimes; or C. Not at all)
2. Do you think wearing the cap helps you to do well in maths? (A. Yes; B. Maybe; or C. Not at all). Why?
3. How did you feel when you wore the hat? (Open-ended question)
4. Did you feel uncomfortable wearing the hat? (A. Yes; B. Sometimes; or C. Not at all)
5. If the hat can help you with maths, will you wear it? (A. Yes; B. Maybe or C. Not at all)

Long-term effects

To assess for any long-term effects of tRNS, I conducted a one-off assessment of children's performance on the video game without tRNS and MALT four months later.

Results

Performance on video game training

Accuracy

I conducted a 2-way ANOVA with Time (Day 1-9) as within-subjects factor, and Group (tRNS, sham) as between-subjects factor. I found that the interaction between Time and Group was significant [$F(8,80)=3.69$, $MSE=.046$, $p=.001$, $\eta^2_p=.27$]. This interaction was due to significant differences between tRNS and sham group from Day 6 onwards, suggesting greater improvements in the performance of tRNS group compared to sham after the first 5 training days (Day 6: $p=.009$; Day 7: $p=.02$; Day 8: $p=.014$; Day 9: $p=.072$; Fig. 2). When I decomposed this interaction by Group, I found that the main effect of Time was not significant [$F(8,40)=2.01$, $MSE=.05$, $p=.07$, $\eta^2_p=.29$]. By contrast, I found a significant effect of Time for the tRNS group, indicating a steeper increase in accuracy with training [$F(8,40)=12.33$, $MSE=.05$, $p<.001$, $\eta^2_p=.71$, linear trend analysis explained 89% of the variance: $F(1,5)=42.06$, $MSE=.076$, $p=.001$].

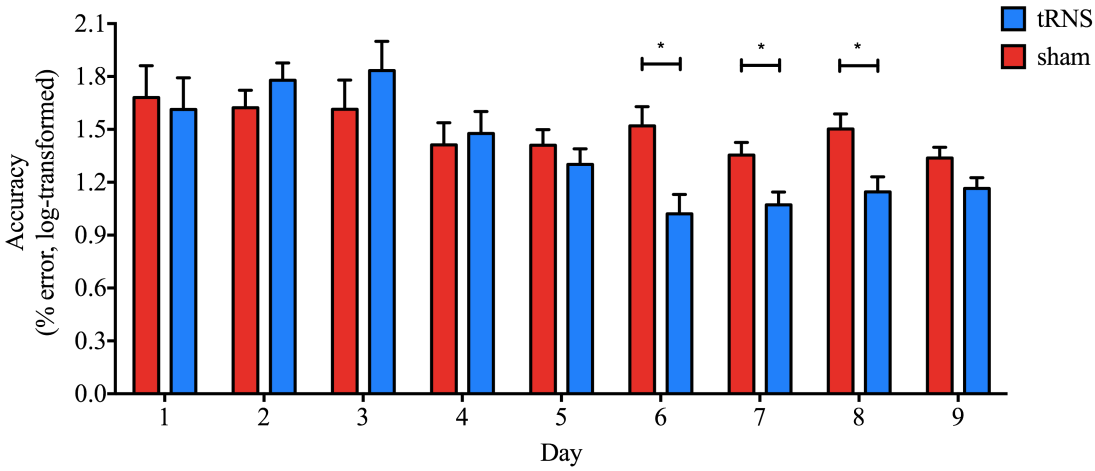

Figure 2 Improved accuracy during training with transcranial random noise stimulation (tRNS) Children in the active, but not sham tRNS group showed significantly improved accuracy during training. Asterisks indicate days where groups differed significantly in accuracy. Error bars represent one standard error of the mean (SEM).

Response times

I further examined whether the accuracy results might reflect speed-accuracy trade-off by running a 2-way ANOVA with the same factors on the RT data. I found a significant interaction between Time and Group [$F(8,80)=3.71$, $p=.001$, $\eta^2_p=.27$]. This was contributed by significantly longer RTs on Day 5 [tRNS (13.12) vs. sham (8.74)] and Day 6 [tRNS (15.76) vs. sham (8.53)]. Given the significant results on accuracy, I examined whether the accuracy results were a result of speed-accuracy trade-off (Pachella, 1974). I ran ANOVA with accuracy averaged over Days 6 to 9 (which has shown group differences in the analysis above) as the dependent variable, Group as the independent variable, and RT (averaged over Days 6 to 9, as for accuracy analyses) as a covariate. I found that the results replicated those on accuracy; there was a main effect of Group [$F(1,9)=6.38$, MSE=.02, $p<.05$, $\eta^2_p=.41$], and crucially, RT was not a significant covariate (p>.41).Together, these findings suggest that improved accuracy observed in tRNS group compared to sham were independent of RT.

Overall levels

It is possible that group differences in accuracy were contributed by the sham group achieving higher and more difficult levels in the game and hence, showed lower accuracy in mapping the numbers given increased difficulty. To examine this, I analysed participants' performance based on the levels completed at the end of each training day. Linear trend analysis indicated that learning was steeper in the tRNS group than the sham group [$F(1,10)=5.9$, $MSE=6.73$, $p<.036$, $\eta^2_p=.37$] (Figure 3).

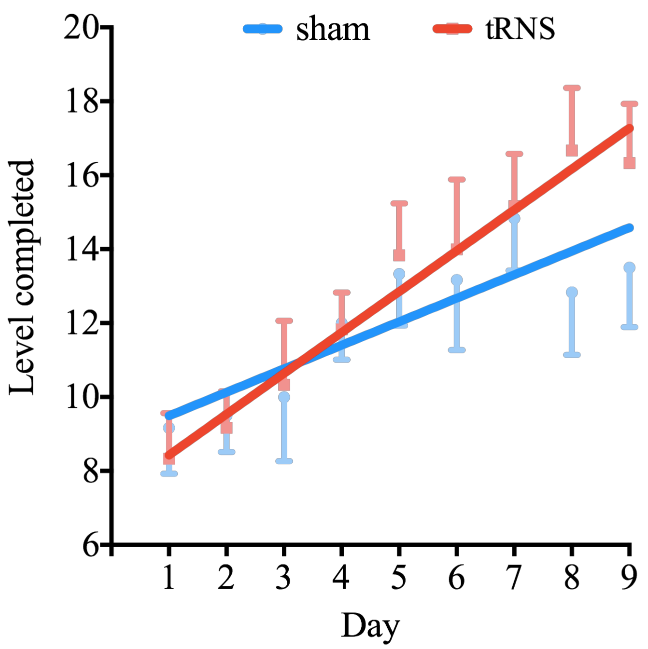

Figure 3 Steeper learning with tRNS. Children who received active tRNS showed a steeper learning slope than those who received sham tRNS. Data points represent the averaged group level at the end of each training day. Error bars indicate one standard error of the mean (SEM).

Working memory

I conducted a 4-way ANOVA with Time (pre- and post-training), Task (Verbal WM, Visuospatial WM) and Order (Forward, Backward) as within-subjects factors and Group (tRNS, sham) as between-subjects factor on the standard scores. I found no significant interactions with Group (all p>.16), indicating no changes in WM capacity attributed to training with or without tRNS, unlike my previous study using tDCS [see Chapter 2, (Looi et al., 2016)].

Transfer effects

I found a positive correlation between percent change in accuracy during training and change in age-equivalence in mathematics derived using the MALT test [non-parametric (Spearman) correlation: r_s=.75, p=.005, 95% confidence intervals (CI) with bias-corrected and accelerated percentile bootstrap method with 10,000 resampling to exclude potential effects of outliers [.12, .97]] (Figure 4A). The same correlation was significant when I analysed the raw scores instead of age-equivalence in mathematics, and when I ran parametric (Pearson) correlation analysis (all r>.64, all p<.03). This consistent relationship indicated that the greater the improvement in accuracy, which was further promoted by tRNS, the greater the improvement on maths performance.

To examine how coupling tRNS with cognitive training influenced MALT scores (i.e., transfer effect), I constructed a path model (Figure 4B). I predicted that improvement in accuracy, which was observed for Days 6 to 9 for those who received active tRNS only would transferred to higher MALT scores. Prior to this set of analyses, I *z*-standardized all scores to allow for inference of effect sizes, and created the interaction term from these standardized scores.

As expected, and consistent with the ANOVA reported earlier, Model 1 showed that Group was not associated with gain in accuracy scores between Days 1 to 5 (β=.11, p=.71) or change in MALT scores (β=.31, p=.28) (Figure 4B). Gain in accuracy across Days 1-5 was not linked to gain in MALT (β=-.05, p=.87), and Group did not moderate the relationship between gain in accuracy between Days 1 to 5 and gain in MALT scores (β=-.27, p=.32).

By contrast, Model 2 showed that Group was negatively associated with gains in accuracy across Days 6 to 9 (β=-.77, p=.001), corroborating the ANOVA results reported earlier that children who received tRNS showed greater gains in accuracy between Days 6 to 9 than those who received sham tRNS. Group was not significantly directly linked to MALT scores (β=.13, p=.77), and the simple main effect of gains in accuracy across Days 6 to 9 was not significantly associated with MALT scores (β=-.22, p=.62). Of interest, I found that Group moderated the relationship between gains in accuracy across Days 6 to 9 and gain in MALT (β=-.99, p=.01). I used an online interaction tool to delineate the interaction term (Preacher, Curran, & Bauer, 2006). Simple slopes analysis revealed that the relationship between gains in accuracy across Days 6 to 9 was associated with improved MALT scores (i.e., transfer effect) only for the tRNS group (tRNS: β=-1.61, p=.02; sham: β=.28, p=.6). The results remained when I included WM scores as a covariate.

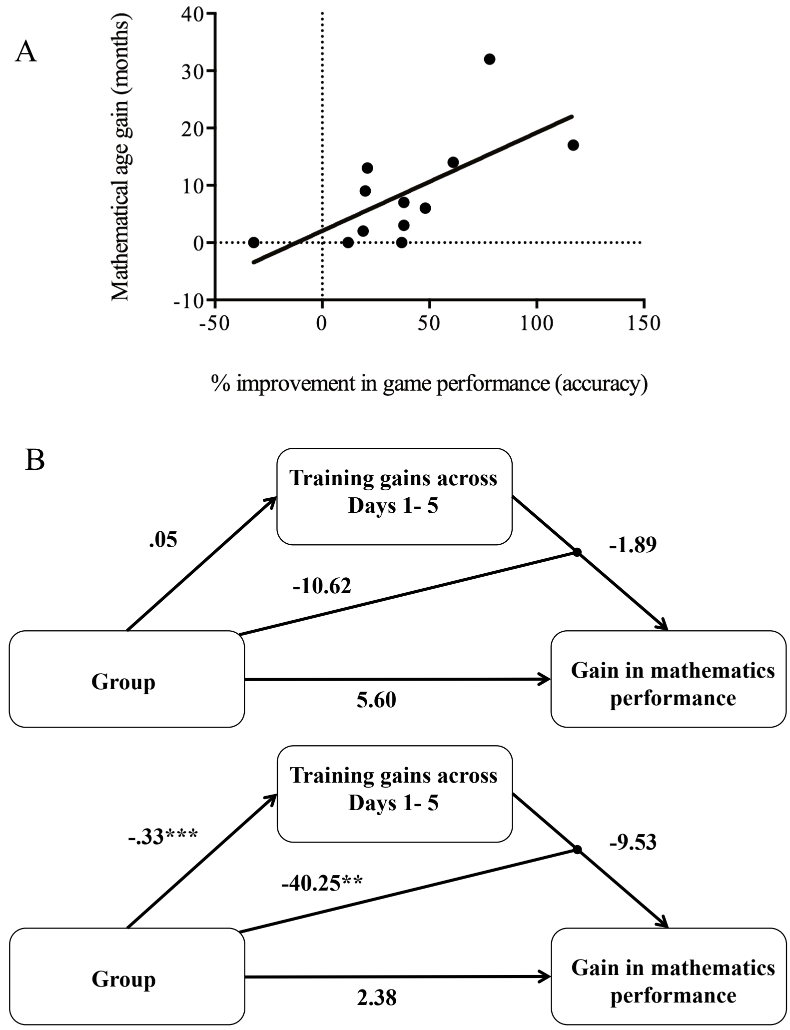

Figure 4 Transfer of training gains to real-life mathematics measure. A) Improvement in training generalised to performance on a standardised diagnostic mathematics test (MALT). Note that while I presented the data values, the correlation was calculated using rank data (Spearman correlation) to account for the small sample size, and to avoid spurious results due to outliers. I did not label the points by group, as I did not find group-related effects. B) Model 1 shows the non-significant effect of tRNS on training between Days 1 to 5 and gain in maths performance (mathematical age-equivalence) derived from the MALT. Model 2 demonstrates the significant correlation between gains in accuracy across Days 6 to 9 and gain in maths performance as indicated by MALT, which was moderated by

group (tRNS vs. sham). Models 1 and 2 reveal the effect of tRNS on transfer, which relies on its effect on cognitive training. For the purpose of transparency, I presented the unstandardised regression coefficients in the figure, and reported the corresponding beta weights in the Results. Note that **=p<.02 and ***=p<.001.

Questionnaire on children's perception of tRNS

Responses of children indicated that they did not discriminate between active and sham condition; all children thought that they received stimulation [$\chi^2(1)=0$, $p=1$] and none thought that wearing the cap did not help. This suggested effective blinding despite the single-blind design of this study. Furthermore, these reports are in line with previous studies on adults that reported higher cutaneous threshold of tRNS compared to other tES (Ambrus et al., 2010; Popescu et al., 2016), and potentially reflecting the lower tRNS current used (.75mA). When children were asked if wearing the cap helps, 4/6 from the tRNS group responded "Yes", 5/6 children from the sham group responded "Yes", and the remaining answered "Maybe" ($\chi^2(1)=.44$, $p=.51$). From the tRNS group, one child reported feeling uncomfortable when wearing the cap, and three children mentioned that they sometimes felt uncomfortable. From the sham group, two children mentioned that they felt uncomfortable sometimes ($\chi^2(1)=1.33$, $p=.25$). They attributed this discomfort to itchiness caused by the strap around the chin. When asked if they would wear the cap if it would help them with maths, all children in the sham group answered, "Yes", while those from the tRNS provided varied responses (Yes: 3/6, Maybe: 2/6, No: 1/6). The child who answered "No" from the tRNS group explained that he did not want to look weird. Mann-Whitney U test indicated no significant difference between the groups (U=9, p=.47). Overall, children's responses did not indicate any attribution of physical side effects to tRNS.

Long-term effects

Four months later, without further tRNS or cognitive training, I found a significant effect of Time [$F(2,12)=6.24$, $MSE=43.3$, $p=.014$, $\eta^2_p=.51$]. Linear trend analysis explained 53% of the variance [$F(1,8)=9.09$, $MSE=46.8$, $p=.017$; quadratic trend: $F(1,8)=2.28$, $MSE=46.8$, $p=.17$]. These findings suggest that improvement in MALT was maintained. Furthermore, I observed the expected maturation of 4 months from formal schooling (Figure 5). At the follow-up, two children did not take part as they had changed school.

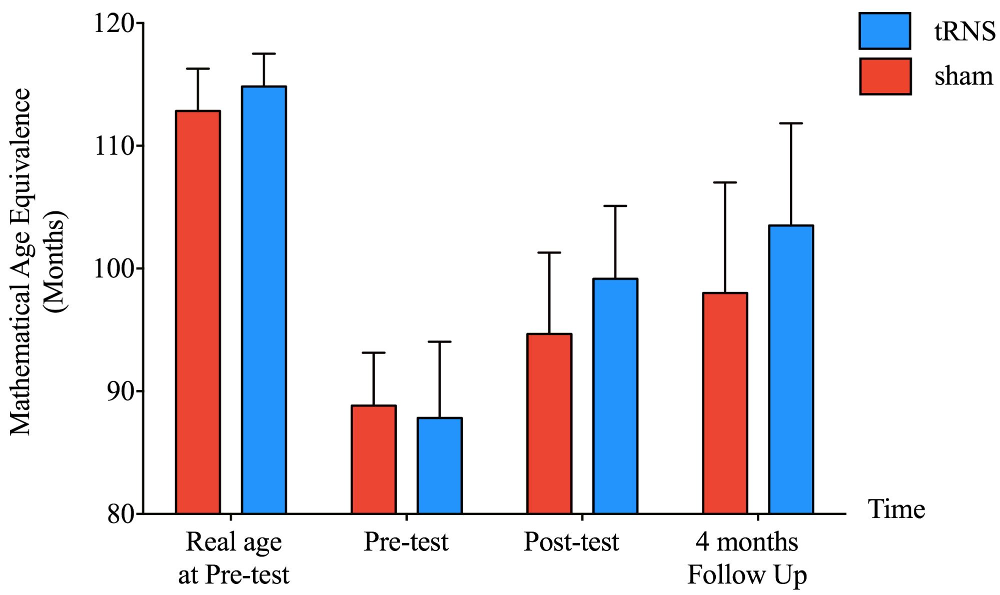

Figure 5 Children's mathematical-age equivalence based on the MALT at pre-test, post-test and 4 months follow up.

Discussion

In the current study, I extended the concept of combining tES and video game training to improve learning and cognition children with MLD. Specifically, I examined whether tRNS during video game training would (1) improve the learning of children with MLD, and (2) increase transfer effects to a real-life task compared to training alone. To my knowledge, this is the first study using tRNS that was conducted in school, a real-world learning environment.

I found that children with MLD who received tRNS showed significantly more accurate performance across training days compared to those who received sham tRNS. This finding is consistent with that of a previous study on healthy adults that showed active tRNS over bilateral dlPFCs improved arithmetic performance compared to sham tRNS (Snowball et al., 2013). More generally, I found that tRNS promoted a steeper learning rate compared to sham, supporting previous findings on healthy adults within the mathematical (Cappelletti et al., 2013; Popescu et al., 2016; Snowball et al., 2013) and non-mathematical domain (Fertonani et al., 2011).

Apart from improved training outcomes linked to tRNS, I found a positive transfer from training gains to children's achievement on MALT, a standardized diagnostic test calibrated to the national curriculum. In line with findings of cognitive training on healthy children in another cognitive domain (Jaeggi et al., 2011), I found that the greater the training outcome, the greater the improvement in mathematical performance on MALT. Crucially, this transfer was modulated by tRNS, corroborating findings based on healthy adults that suggest tRNS during training promote the transfer of numerical training gains to related materials (Cappelletti et al., 2013; Popescu et al., 2016; Snowball et al., 2013) (Figure 4B). Consistent with tRNS studies on healthy adults in the numerical domain (Cappelletti et al., 2013; Popescu et al., 2016; Snowball et al., 2013) and WM domain (J. Holmes, Byrne, & Gathercole, 2016), but in contrast to my previous study using tDCS (Looi et al., 2016), I did not find any transfer effects to WM, suggesting the lack of transfer beyond trained domain (Melby-Lervåg & Hulme, 2013). Further research could examine whether transfer effects beyond trained domain is affected by the choice of tES. Since that training gains generalised to a standardised diagnostic tool, these findings might offer implications for special education.

It is worth noting that the current study was challenged by practical difficulties and sample size constrains, similar to early-stage innovative clinical and translational research (Bacchetti, Deeks, & McCune, 2011). As the tRNS software was not equipped with a double-blinding function at the time of study, it was difficult to conduct a double-blinded study given that I was responsible for study design, and participant recruitment, selection, and testing with the support of the school's occupational therapist at school. However, the current results are unlikely to have been biased for three reasons. First, training was automated and therefore limited my involvement during children's training. Second, behavioural changes did not surface at the beginning of training but rather, towards the end. Third, improvements found were not general; it was specific to the mathematical domain, as there were no changes in WM capacity. Furthermore, the novelty of tRNS for paediatric use and hence, lack of safety records and scientific precedent of its application (especially in the context of cognitive training, whereby tRNS is applied for more than a single session) contributed to the lack of support from schools and difficulty in recruiting a larger sample size.

To improve statistical power, I minimised error variance by controlling for several parameters across groups (Table 1), conducted recruitment and training in the same school. Despite the small sample size, current results survived rigorous statistical analyses that included parametric and non-parametric tests using the bias-corrected and accelerated percentile bootstrap method with 10,000 resamples, and *t*-test, which was originally designed for small sample sizes (Student, 1908). Moreover, the current results of training gains and transfer effect mirror those of tRNS during cognitive training studies on healthy adults (Cappelletti et al., 2013; Popescu et al., 2016; Snowball et al., 2013). Finally, while power and sample size are critical to the reliability of research (Button et al., 2013), it has also been cautioned that neglecting the conceptual and practical difficulties of power-based sample size planning of novel approaches could hinder innovation and translation (Bacchetti, 2013). Therefore, it has been recommended that early-stage practical research should not overrule cost-efficiency and feasibility (Bacchetti, 2013).

In sum, findings from the current study contribute insights into the novel concept of applying tRNS during cognitive training to ameliorate neurodevelopmental disorders. In particular, this study tackles the ethical dilemma of depriving a considerable population of children of potentially improved cognitive abilities, which could lead to significant individual and socioeconomic impact (Krause & Cohen Kadosh, 2013). These experimental data could fuel on-going debates that lacked empirical evidence. At the same time, they raise open questions that are critical to understanding the mechanisms of and potential of brain stimulation use in children, topics that are of scientific and societal interests and concern (Davis, 2014; Maslen, Earp, et al., 2014). The current findings call for systematic replications involving randomised double-blind controlled studies on larger samples, different educational/cultural systems, physiological data on the underlying neural and cognitive mechanisms, and children with other atypical developmental conditions to further this line of enquiry (Krause & Cohen Kadosh, 2013; Vicario & Nitsche, 2013). Considering the growing public interest and use of brain stimulation for cognitive enhancement (Fitz & Reiner, 2013), it is worth noting that the current 'proof-of-concept' findings are aimed at serving as a basis for further scientific investigations, but not support or justification for tRNS application outside the experimental context. While I did not find any evidence that would raise safety concerns, children the current study were carefully selected and strictly assessed for their eligibility to receive brain stimulation. Randomised-controlled studies with larger sample sizes by different laboratories are needed to monitor for any side effects, which has been associated with other forms of tES (Brem et al., 2014). Further research is needed to examine the potential and value of tRNS as a tool for understanding and intervening with atypical neurodevelopmental conditions such as learning disabilities.

Chapter 4

Improving learning and cognition of the aging brain using a numerical video game and transcranial random noise stimulation

Abstract

Aging-related cognitive decline is a global concern, given the unprecedented growth of aging population with longer lifespans compared to previous generations. Based on the promising findings on healthy adults and children with learning disabilities (Chapters 2 and 3, respectively), I explored the use of tRNS and a video game for improving learning and cognition in older adults. The current video game is an adaptation of the previous version (in Chapter 2) for use on a tablet PC (iPad). The idea is to improve its usability for older adults that are associated with reduced motor coordination and mobility. In the current double-blind study, older adults (n=61) underwent fractions training for 2 days of 30 minute-session, while receiving 1mA of active or sham tRNS. I found that active tRNS during training promoted quicker and more accurate performance compared to sham tRNS. Notably, those who received active tRNS did not show cognitive costs indicated by speed-accuracy trade-offs during training, and negative transfer effects after training shown by the sham group. Questionnaire responses indicated no immediate perceived cognitive or physical side effects attributed to tRNS, suggesting that tRNS during cognitive training could be effective for modulating learning and cognition of the healthy aging population.

Introduction

Cognitive deterioration due to aging that compromises learning and cognition is linked to decreased neuroplasticity (S.-C. Li et al., 2006) and cognitive resources (Craik & Byrd, 1982; S. Jones et al., 2006; D. C. Park, 2000; D. C. Park & Bischof, 2013; Salthouse, 1988a). The aging brain is thought to adapt by switching to more "affordable" strategies via reallocation its cognitive resources (D. C. Park & McDonough, 2013; Raz, 2009). Such modifications have been associated with costs indicated at multiple levels, from decreased signal-to-noise ratio in the neural system (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; S.-C. Li, Lindenberger, & Sikström, 2001; MacDonald, Nyberg, & Bäckman, 2006; Welford, 1981) to decline in processing speed (Salthouse, 1996) and cognitive abilities such as mathematical skills (Hartshorne & Germine, 2015; Raz, 2009). Therefore, interventions that could promote neuroplasticity and optimise cognitive resources without incurring cognitive and physical costs could be ideal for counteracting cognitive decline and improving cognitive functions (Brem et al., 2014; Davis, 2014; Iuculano & Cohen Kadosh, 2013; S. Jones et al., 2006; D. C. Park & Bischof, 2013).

Cognitive training has shown the potential for improving a range of cognitive abilities of the aging brain [for meta-analyses see, (Bartrés-Faz, Rossi, & Pascual-Leone, 2016; Kelly et al., 2014)], which are accompanied by neuroplastic changes in brain volume and activity [for a review, see (D. C. Park & Bischof, 2013)]. While the field of cognitive training focuses on the challenge of promoting positive transfer effects (Toril et al., 2014), especially "far-transfer" to materials that are less similar in nature or content to cognitive training (Melby-Lervåg & Hulme, 2013), few have drawn attention to the negative transfers (Link et al., 2013) or cognitive costs associated with training (Persson, Welsh, Jonides, & Reuter-Lorenz, 2007). Considering the decreased neuroplasticity and cognitive resources of the aging brain (Craik & Byrd, 1982; D. C. Park, 2000b; Salthouse, 1988a), it might be especially relevant to monitor for any cognitive costs linked with training.

To date, tRNS has been mainly shown to further improve training outcomes of healthy adults (Cappelletti et al., 2013; Snowball et al., 2013), and more recently, of older adults within the range of 5 days (Cappelletti et al., 2015). Reported effects however, were derived from simple training tasks with little resemblance to learning in the real-world (e.g., non-adaptive, without feedback). Of concern, tRNS led to not only positive, but also negative transfer effects (Cappelletti et al., 2015), mirroring cognitive costs associated with the use of tDCS (Iuculano & Cohen Kadosh, 2013; Sarkar et al., 2014). Such findings trigger questions on the safety, costs-to-benefits, and ethics of tRNS usage, whether for treatment, cognitive enhancement (Hamilton et al., 2011; Iuculano & Cohen Kadosh, 2013), or as preventive intervention.

In the current study, I examined (1) the effects of tRNS on the training performance of older adults compared to training alone, and (2) how tRNS might influence transfer effects from training to non-trained, but related real-world materials. I also monitored for other potential cognitive and physical side effects of tRNS on this population using a questionnaire. My training targets the mathematical domain, which could have implications for older adults given the decline of mathematical abilities from the age of 50 (Hartshorne & Germine, 2015) that compromises their independence in decision-making on health (Reyna, Nelson, Han, & Dieckmann, 2009) and finance (Lusardi, 2012) matters. The current training is on fractions mapping, using a gamified version of the game reported in Chapter 2. Furthermore, instead of requiring bodily movements during mapping, the current version was adapted for use on a tablet PC (iPad) by a professional game developer (Locked Door Puzzles, Bristol). This training mode was chosen to account for the reduced motor coordination and mobility associated with older adults, and to improve its usability in real-life. Healthy older adults trained for two consecutive days (30 minutes each session) to minimise time commitment, shown to support better performance amongst older populations (Lampit et al., 2014). I used tRNS, thought to increase signal-to-noise ratio via stochastic resonance to improve neural signal detection (Miniussi et al., 2010; van der Groen & Wenderoth, 2016), which might be potentially relevant to older adults given age-related increase in neural noise (Cappelletti et al., 2015; Welford, 1981). Moreover, tRNS during arithmetic training on young adults has been associated with reduced and more efficient brain metabolism (Snowball et al., 2013), suggesting its potential for optimising neural resources. Experimentally, tRNS offers more effective participant and experimenter blinding, as it induces less cutaneous sensation compared to other forms of tES (Ambrus et al., 2010). I applied tRNS over the bilateral dorsolateral prefrontal cortices (dlPFCs), as they are thought to be implicated during (1) fractions training in young healthy adults [as shown in Chapter 2, (Looi et al., 2016)], mathematical cognition (Arsalidou & Taylor, 2011); and (2) a range of executive functions (Diamond, 2013) involved during cognitive training and mathematical processing, which might enable transfer effects to occur through overlapping cognitive resources (Taatgen, 2013). Furthermore, dlPFCs which were associated with processing cognitive resource allocation and resource-demanding tasks have shown the greatest age-related decline (Raz et al., 2005). I pseudo-randomly assigned older adults (n=61) into two groups: to receive either active tRNS or sham (placebo) tRNS during video game training based on a range of variables (Table 1). I assessed their training performance, and transfer effects on tasks that shared similar processes with training, before and after training. In line with the theoretical and experimental development in the field of cognitive training at the time, I assessed for "near-" and "far-" transfer effects (Melby-Lervåg & Hulme, 2013) by measuring older adults' performance on tasks that are similar (addition, simple division and complex division) and different (WM) in nature (i.e., content, format) to the current training.

Based on previous tRNS studies (Cappelletti et al., 2013; Cappelletti et al., 2015; Snowball et al., 2013), I hypothesized that compared to training alone, (1) tRNS during training would lead to better training outcomes amongst older adults, and that (2) tRNS would influence transfer effects to non-trained materials that share similar processes with our fractions training such as division, but not addition.

Methods

Participants

Older adults (n=61) aged between 50-78 (mean=64 years 4 months±SD=6 years 6 months) with no reported history of neurological/psychiatric disorders, or under medication targeted to the central nervous system participated in the current study. I pseudo-randomly allocated older adults to two groups: receiving either active tRNS or sham tRNS based on their baseline mathematical ability (using the WIAT-II^{UK}), age, gender, and handedness (Table 1)[4]. I recruited older adults from Oxfordshire[5].

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[4] This responsibility of group allocation was shared with my lab colleague at the time, now Dr. Beatrix Krause, who is a co-author on the manuscript of the current study.

[5] Recruitment was conducted over the course of 2 years, with the contribution of Dr. Beatrix Krause, and Final Honour School students whom I supervised as Day-to-day supervisor at

They gave their informed consent, and were medically screened each day before starting the experiment[6]. Each participant was reimbursed £50 for his/her participation in this study. I received ethical approval from the Central University Research Ethics Committee, University of Oxford to conduct this study. This was a double-blinded study; neither the experimenter(s) nor the participants were given information about participants' group allocation.

Controlled Variable/Group	**Active tRNS**	**Sham tRNS**	**Differences between groups**
Age	64.4 ± 6.6	64.2 ± 6.6	t(59)=.131, *p*=.896
Gender	12 females, 19 males	12 females, 18 males	$\chi^2(1)$=.011, *p*=.918
Mathematical Ability (WIAT-II)	109.8 ± 13.5	108.7 ± 15.3	t(59)=.29, *p*=.773
Handedness	3/31 left-handed	3/30 left-handed	$\chi^2(1)$=.002, *p*=.966
Working memory (SD)			
Verbal			
Forward	6.1 (1.1)	5.9 (1.1)	t(56)=.55, *p*>.59
Backward	4.3 (1.3)	4.5 (0.9)	t(56)=-.59, *p*>.56
Visuospatial			
Forward	4.3 (0.6)	4.6 (1.1)	t(56)=-1.1, *p*>.29

the time: Aneesha Chauhan, Natalia Cotton, Ealish Swift and Charlotte Browne, all co-authors on the manuscript of the current study.

[6] The data collection spanned 2 years, and was undertaken by Aneesha Chauhan, Natalia Cotton, Ealish Swift and Charlotte Browne under the partial supervision of Dr. Beatrix Krause, and myself.

Backward	4.0 (0.8)	3.9 (0.7)	t(56)=.35, *p*>.73

Table 1. Older adult participants were matched across active tRNS and sham tRNS groups by their age, gender, mathematical abilities, and WM capacity.

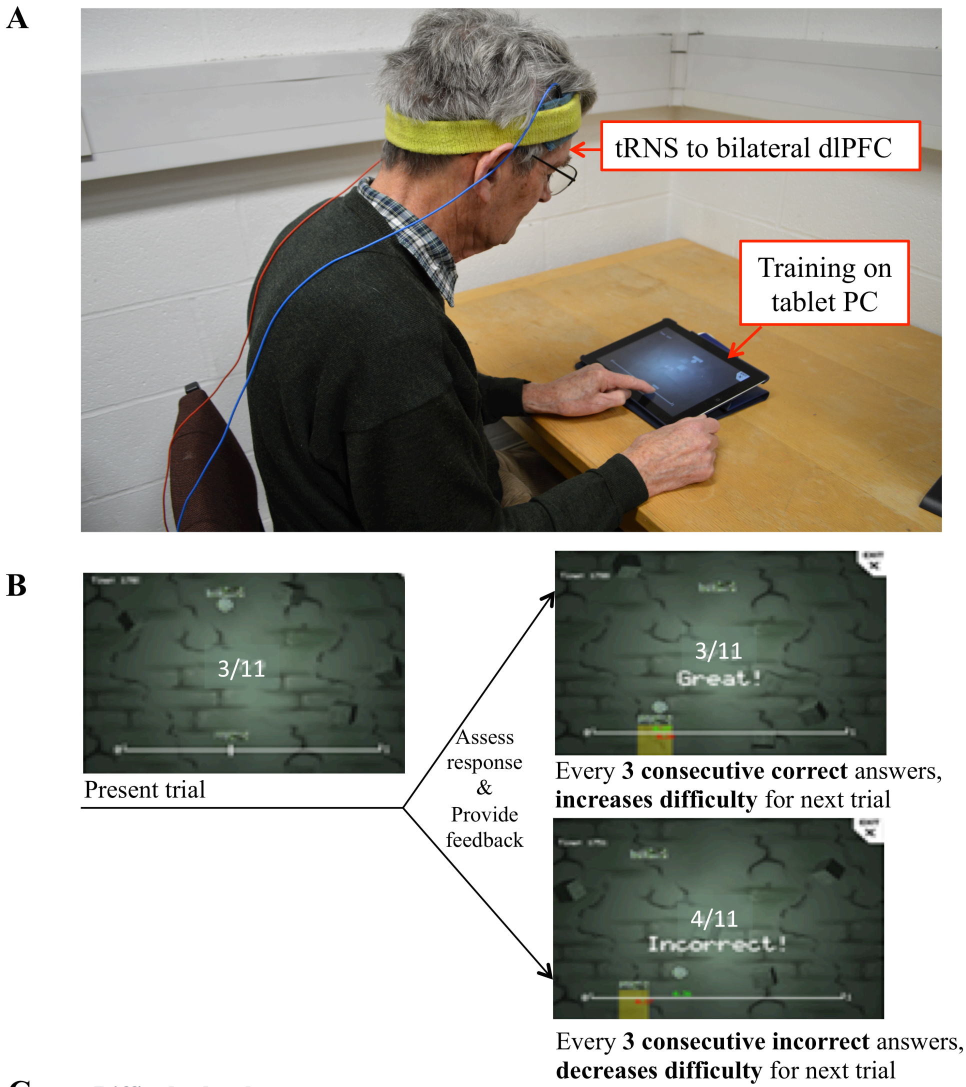
Transcranial random noise stimulation (tRNS)

I pseudo-randomly assigned participants into either the active or the sham tRNS group based on variables in Table 1. Throughout the 2 days of 30 minutes training, the active tRNS group received 1mA of high frequency tRNS (100-640Hz) over their bilateral dlPFCs (F3 and F4 based on the International 10-20 system) delivered by two 5x5cm saline-soaked sponge electrodes, wired to the DC-Stimulator Plus (NeuroConn, Germany). The sham group received tRNS following the identical parameters, but for a total of 30 seconds only (15 seconds ramp-up and 15 seconds ramp-down, at the start and end of training respectively). This brief stimulation is thought to sufficiently induce a tingling sensation on the stimulation sites on the scalp, simulating "active" tRNS sensations for participant blinding purposes, but negligible effects at the neural level (Chaieb et al., 2009).

Tablet-based video game training

Older adults mapped fractions on a virtual number line that was presented in the form of a video game on a tablet PC (iPad). Similar to the rationale in Chapter 2, training was focused on fractions, as competence with fractions have been shown as strong predictors of mathematical achievement in younger populations (Bailey et al., 2012; Siegler & Ramani, 2008). To map the location of a specific fraction prompted in the center of the screen, older adults dragged their index finger across the virtual line presented on the screen to their perceived fraction-equivalence position (Figure

1). To indicate their response, they lifted their finger from the screen. Operating on the same concept, this tablet game was adaptive; it automatically adjusted the game difficulty by altering the Levels (represented by the level of complexity of the fractions to be mapped) and Precision (represented by the degree of accepted deviation from a target to be considered a "correct" response). Specifically, within each Level, there were 4 Precision levels (7%, 6%, 5%, 4%). Every 3 consecutive correct answers led to a trial with a higher Precision requirement, from 7%, 6%, 5% to 4%, followed by a higher Level of fractions complexity (e.g., from Easy to Medium). By contrast, every 3 consecutive incorrect answers demoted a trial to a immediate lower Precision requirement, e.g., from Precision 4%, 5%, 6% to 7% within the same Level (e.g., Medium), followed by the previous Level of fractions complexity (e.g., Easy, at Precision 4%) (Figure 1). This game recorded the response times (RT), accuracy, and the number of levels attempted. Participants were given the instructions to map fractions as accurately and as quickly as they could.



C

Difficulty levels

Type	Precision	Example fractions
Easy	± 7% ± 6% ± 5% ± 4%	1 □ □ □ □ 2 3 4 5 6
Medium	± 7% ± 6% ± 5% ± 4%	□ □ □ □ □ 7 8 9 11 13
Hard	± 7% ± 6% ± 5% ± 4%	□ □ □ □ □ 15 16 17 18 19

Figure 1 Combining tRNS and tablet-based numerical training to improve learning of healthy older adults A) Experimental setup consisted of cognitive training using a tablet PC, while receiving tRNS over bilateral dlPFCs. Older adults mapped fractions on a virtual number line by adjusting the position of their fingers on the screen.

Response was registered when participants lifted their finger from the screen. B) Sequence of a trial; the difficulty of each trial was automatically adjusted to participants' performance. Feedback on the exact position of each target fraction on the number line was given for both correct and incorrect responses immediately after each response. C) Fractions prompted during the game was dependent on participants' performance. Difficulty of trials was adjusted as a function of fraction complexity or Level (Easy, Medium, Hard), and Precision (allowed deviations from the target; ±7%, ±6%, ±5% and ±4% of the number line range). The idea was to challenge participants to map fractions at their maximal capacity (shortest RT and highest accuracy).

Cognitive assessments

Mathematical abilities

Participants' mathematical abilities were examined using a standardized mathematical assessment (WIAT-II, UK). They were tested using the Numerical Operations subtest that assessed written calculation abilities, and the Mathematical Reasoning subtest that assessed verbal word problem solving. The mean standard scores for each group are presented in Table 1.

Working memory (WM)

Standardised tests were used to assess verbal and visuospatial WM capacities. Verbal WM was assessed using Digit Span. Participants were asked to listen to a series of digits that I read aloud, and then to verbally repeat the sequence. The first trial consisted of 2 digits. With every 2 trials, the span increased by one digit. Visuospatial WM was assessed using Corsi Blocks. Participants were asked to observe a sequence that I tapped on a series of blocks, and then to repeat the tapped sequence. The first sequence involved 2 blocks. With every 2 trials, the sequence increased by one block. Each task was terminated when participants gave 2 consecutive incorrect responses. The mean standard scores for each group are presented in Table 1.

Transfer tasks

To assess for any near-transfer effects from training, 3 tasks of 18 arithmetic problems each were designed and implemented (see Supplemental Methods: Transfer tasks at the end of this chapter). These tasks were sets of Addition, Simple division and Complex division, respectively. Participants were asked to solve as many problems as possible on each task within 10 minutes. They were allowed to leave out questions, but not allowed to revisit them. The number of correct trials was measured. In the event that participants completed all sums in less than 10 minutes, their RT was recorded. There were no group differences in the initial performance on these 3 transfer tasks (Table 2). To assess for far-transfer effects, participants' performance on the WM tasks as described in the previous section was examined before and after training.

Task/Group	Active tRNS (mean ± SD)	Sham tRNS (mean ± SD)	Group differences
RT			
Addition	194.17 ± 68.95	219.00 ± 80.61	t(56)=-1.26, *p*=.20
Simple division	514.07 ± 132.99	452.21 ± 161.41	t(54)=1.57, *p*=.12
Complex division	346.93 ± 148.65	369.08 ± 144.52	t(52)=-.55, *p*=.58
Accuracy			
Addition	94.83±6.95	93.87±7.91	t(56)=.49, *p*=.63
Simple division	91.22±8.47	91.21±10.16	t(54)=.002, *p*=1.0
Complex division	76.54±18.87	67.64±26.62	t(52)=1.43, *p*=.16

Table 2 Baseline performance on transfer tasks, RT (seconds, RT). Active tRNS and sham tRNS groups did not differ in RT or accuracy of performance on the transfer tasks before cognitive training. Note that up to 4 participants were excluded (tRNS=1, sham=3), as they were unable to solve any of the Simple and/or Complex Divisions at pre- and/or post-training

Questionnaire on side effects

To monitor for any cognitive or physical side effects attributed to tRNS, participants were asked to complete a short questionnaire. Not all participants completed this questionnaire (total=40; active tRNS=19), as it was developed in the later stages of this study. The questionnaire required participants to enter a value to indicate whether they felt any of the 9 most commonly listed symptoms (i.e., headache, neck pain, scalp pain, scalp burns, sensations under the electrode such as tingling, itching, burning and pain, skin redness, sleepiness, trouble concentrating, change in mood) and/or list 'other' sensations that they felt. They were asked to rate these symptoms on a scale of four; 1: Absent; 2: Mild; 3. Moderate; and 4: Severe, after each session of training, with or without tRNS.

Procedure

Older adults took part in the current study for 3 days that lasted for 5 hours in total (Table 3).

Day	**Tasks**	**Time**
1	Cognitive assessments (Pre-test), in the order of: • Mathematical ability (WIAT-II^{UK}) • Transfer tasks (Addition, Simple division, Complex Division) • Working memory (Digit Span, Corsi Blocks)	2 hours
2	Tablet-based cognitive training with active/sham tRNS Questionnaire on side effects	0.5 hour
3	Tablet-based cognitive training with active/sham tRNS Cognitive assessments (Post-test, same as pre-test and in the same order) Questionnaire on side effects	2.5 hours

Table 3 Participants participated in the current study, which took 3 days, 5 hours in total.

Statistical analyses

I used IBM SPSS statistics to perform all statistical analyses with the threshold for significance set at $p<.05$. I removed 3 outliers from the analyses; 2 from the active tRNS group due to lack of progression in the game (achieved 5 levels and 8 levels in total within the 2 days of training compared to the average of 18 levels in total, SD=4 across all participants), and 1 from the sham group due to RT above 3 SD from the mean. For analyses on RT and accuracy, I included trials up to Level 2 (Level 1=Easy; 2=Medium) to include as many participants as possible in my analyses while maintaining a factorial design, given that 9 participants did not complete Level 3 (Hard). To take all levels into account, I conducted an analysis on the levels completed, with the levels of completed as the dependent variable. I calculated the accuracy of participants' responses based on the mean of [(Participants' Estimate – Target Fraction Value)/Number range of each trial's number line], which was adopted in studies using similar tasks (Siegler & Booth, 2004) and in my previous studies [Chapters 2, (Looi et al., 2016) and 3)]. I analysed all data from training (RT in seconds, accuracy, levels completed) and cognitive assessments using Analysis of Variance (ANOVA). I ran analyses to examine speed-accuracy trade-off during training, and transfer effects from training using parametric correlational analysis with 95% confidence intervals (CIs), bias-corrected and accelerated percentile bootstrap method, with 10,000 resampling. I further examined the transfer effects through moderation regression analysis using PROCESS (by Andrew F. Hayes, http://www.afhayes.com), which determines whether a third variable influences the direction/strength of the relationship between a predictor and a dependent variable (Baron & Kenny, 1986). Based on the findings of tRNS on transfer effects in previous studies (Cappelletti et al., 2015; Snowball et al., 2013), I ran a moderation regression analysis to assess whether receiving active or sham tRNS affected the relationship between training and performance on transfer tasks.

Results

Training performance

Response times

I conducted a 4-way ANOVA with Time (Day 1, Day 2), Level (1,2) and Precision (7%,6%,5%,4%) as within-subject factors, and Group (tRNS, sham) as between-subject factor. I found that participants' responses were quicker on Day 2 (56.09±SD=19.83) than Day 1 (60.09± SD=19.60) [$F(1,56)=5.731$, $p=0.020$, $MSE=10.08$, $\eta^2_p=0.093$]. Of interest, I found that the interaction between Group, Level, and Precision was significant [$F(3,168)=3.14$, $p=0.027$, $MSE=1.50$, $\eta^2_p=0.05$]. I ran further analysis, decomposed by Precision and found a significant interaction between Group and Level in Precision 7% [$F(1,56)=11.55$, $p=.01$, $MSE=1.36$, $\eta^2_p=.11$], 6% [$F(1,56)=4.0$, $p=.050$, $MSE=1.32$, $\eta^2_p=.07$], and 5% [$F(1,56)=6.47$, $p=.014$, $MSE=1.88$, $\eta^2_p=.10$], but not Precision 4% ($p>.69$) (Figure 2). Independent *t*-tests further revealed that these significant interactions between Group and Level stemmed from stronger effects in Level 2 (Medium level) than Level 1 (Easy level) (Table 4; for data on mean RTs, see Table 5).

Precision	**Level 1**	**Level 2**
7%	t(56)=-1.91, *p*=.061, Cohen's d=-.50	t(56)=-3.43, *p*<.001, Cohen's d=-.90
6%	t(56)=-2.02, *p*=.048, Cohen's d=-.53	t(56)=-2.69, *p*=.009, Cohen's d=-.71
5%	t(56)=-2.15, *p*=.036, Cohen's d=-.56	t(56)=-3.14, *p*=.003, Cohen's d=-.82
4%	t(56)=-3.51, *p*=.001 Cohen's d=-.94	t(56)=-2.61, *p*=.012 Cohen's d=-.70

Table 4 Active tRNS group showed quicker responses than the sham tRNS group during training in various Precisions, with more pronounced effects in Level 2 than Level 1.

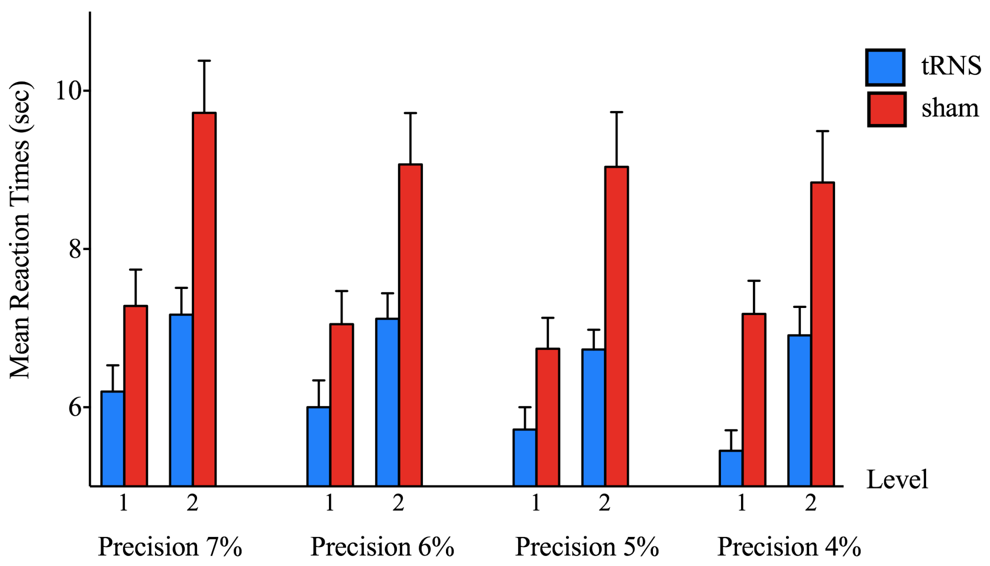


Figure 2 Three-way interaction between Group, Level, and Precision on video game training RT. Interaction was due to a significant two-way interaction between Group and Level in Precisions 7%, 6% and 5%. Active tRNS group showed quicker

responses than the sham group in these Precision levels. Note that compared to sham, they were also quicker in Precision 4% (*p*=.003), but there was no interaction with Level (*p*>.69). Error bars represent one standard error of mean (SEM).

Level/Group	**Active tRNS (mean ± SD)**	**Sham tRNS (mean ± SD)**	**Group differences**
Level 1, Precision 7%	6.01 ± 2.07	7.66 ± 2.61	t(1,56)=-2.67, *p*=.010
Level 1, Precision 6%	5.69 ± 1.85	7.54 ± 2.46	t(1,56)=-3.24, *p*=.002
Level 1, Precision 5%	5.50 ± 1.46	7.12 ± 2.18	t(1,56)=-3.33, *p*=.002
Level 1, Precision 4%	5.57 ± 1.71	7.37 ± 2.40	t(1,56)=-3.29, *p*=.002
Level 2, Precision 7%	7.27 ± 2.75	9.76 ± 3.54	t(1,56)=-3.00, *p*=.002
Level 2, Precision 6%	6.99 ± 2.20	9.21 ± 3.89	t(1,56)=-2.69, *p*=.010
Level 2, Precision 5%	6.83 ± 2.33	9.15 ± 4.32	t(1,56)=-2.55, *p*=.014
Level 2, Precision 4%	6.90 ± 2.60	8.78 ± 3.73	t(1,56)=-2.23, *p*=.030

Table 5 Training Mean RT (seconds) per trial between groups for each precision of each level.

Accuracy

I conducted a 4-way ANOVA with the same factors used in RT analyses. I found that the only significant interaction with Group was the 2-way interaction between Group and Time [$F(1,56)=12.46$, $p=0.001$, MSE=.001, $\eta^2_p=0.18$]. Independent *t*-tests revealed that on Day 1, the sham group was more accurate than the active tRNS group in fractions mapping, but on Day 2, the trend was (marginally) reversed [Day 1: $t(56)=2.40$, $p=.02$, Cohen's d=.64; Day 2: $t(56)=-1.77$, $p=.083$, Cohen's d=.47; for mean accuracies, see Table 6]. Within each group, paired *t*-tests showed that the active tRNS group became significantly more accurate in fractions mapping with training, while the sham group showed became significantly less accurate with training (Figure 3; Table 6) [tRNS: $t(28)=2.52$, $p=.018$; sham: $t(28)=-2.50$, $p=.019$].

Time/Group	Active tRNS (mean ± SD)	Sham (mean ± SD)
Day 1	.04 ± .01	.03 ± .01
Day 2	.03 ± .01	.04 ± .01

Table 6 Average training accuracies [(Participants' Estimate – Target Fraction Value)/ Number range of each trial] between groups for each training day.

Speed-accuracy trade-off analysis

Since the tRNS group showed shorter RTs but lower accuracy on Day 1 compared to the sham group, I assessed whether these results were due to speed-accuracy trade-off. I ran a bivariate correlation between Day 1 RT and accuracy of the active tRNS group. The correlation between these variables was not significant (Pearson: $r=0.10$, $p=0.61$). I also examined the effect of Day 1 accuracy (which showed a better performance for sham group) on the 3-way interaction found with RTs (which showed better performance for tRNS group) by re-running the ANOVA on RT using Day 1 accuracy as the covariate. I found that accuracy on Day 1 was not a significant covariate, p>.76, and it did not interact with Day, Level or Precision, p>.21. The interaction between Group, Level, and Precision remained significant [$F(3,165)=3.13$, $p=0.027$, MSE=1.52, $\eta^2_p=0.054$] and followed the same pattern as reported earlier. These results indicate that accuracy on Day 1 did not influence RT.

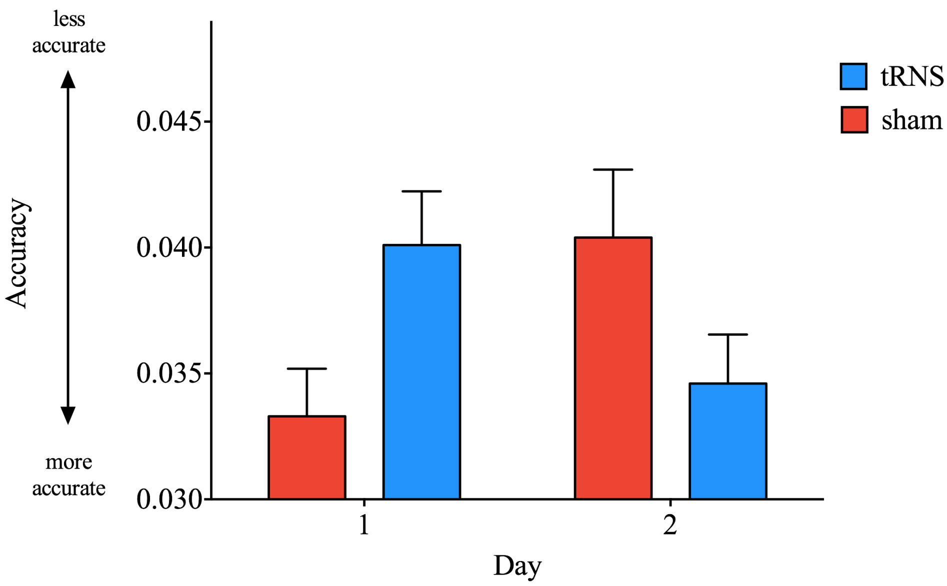


Figure 3 Interaction between Group and Time in accuracy (mean absolute deviation of response from target fraction). On Day 1, the sham group showed more accurate performance compared to the active tRNS group. However, on Day 2, a reversed trend was found; the active tRNS group was marginally more accurate in mapping compared to the sham. Across training, the active tRNS group became more accurate in fractions mapping, while the sham group became less accurate. Note that group differences in accuracy on Day 1 was not explained by speed-accuracy trade-off (p>.31), or group differences in baseline mathematical abilities pre-training (p>.77).

However, it is possible that the sham group's reduced accuracy with training was due to a trade-off for quicker responses, as both groups were quicker on Day 2. To examine this, I performed a correlation analysis on the gain in RT across days (Day 2-Day1 RT) and gain in accuracy (Day 2-Day1 accuracy) of the sham group. Indeed, I found a significant negative correlation [Pearson $r=-.53$, $p=.003$; 95% CIs (-.79,-.12)], which suggests that reduced accuracy of the sham group across training was a trade-off for quicker responses. This relationship remained significant independent of age, years of education and levels achieved in the game (all $p<.006$). Of interest, this was not the case for the tRNS group ($r=-.11$, $p=.58$). I found that the correlations differed significantly between Groups ($Z=-2.00$, $p<.05$) (J. Cohen, Cohen, West, & Aiken, 2003).

Overall levels completed

To account for all levels achieved during training (beyond the two levels included in the ANOVAs on RT and accuracy), I analysed participants' performance based on the highest level completed at the end of each training day (Max 28 levels; 7 Levels x 4 Precision). I conducted a 2-way ANOVA on Time (Day 1, Day 2) and Group (tRNS, sham). I found a marginal main effect of Group $F(1,56)=3.90$, $p=.053$, $MSE=27.23$, $\eta^2_p=.065$, indicating that the active tRNS group achieved marginally higher levels than the sham group (18.66±SD=3.58) vs. (16.74±SD=3.80). The main effect of Time was significant [$F(1,56)=5.31$, $p=.025$, $MSE=6.44$, $\eta^2_p=.087$], which suggests that both groups achieved higher levels on Day 2 (18.24±SD=4.03) than on Day 1 (17.16±SD=4.33). Other effects were not significant, all $p>.74$.

Transfer tasks

I ran a 2-way ANOVA on RT and accuracy, with Task (Addition, Simple division, Complex division) as within-subject factors, and Group (tRNS, sham) as the between-subject factor. To measure change in performance between pre- and post-training, I controlled for pre-training RT as a covariate instead of subtracting these values from post-training as this method has been recommended as more rigorous and better-suited to the current study design (Edwards, 2001; Van Breukelen, 2006). Note that I excluded 4 participants (active tRNS=1, sham tRNS=3), as they were unable (lack of ability) to solve any of the Simple and/or Complex Divisions at pre- and/or post-training (for group baselines in RT and accuracy, see Table 2).

Response Times

I calculated the RT per problem in each task by dividing the total time taken by the number of questions attempted. I found that the effect of Group was not significant, and did not interact with Task (p>.17).

Accuracy

I defined accuracy as the number of correct/attempted trials x 100%. I found a significant interaction between Group and Task [$F(2,102)=4.96$, MSE=106.18, p=.019, η^2_p=.089; Greenhouse-Geisser corrected given sphericity violation (Girden, 1992)] which stemmed from the effect of Group on Complex Division, [$F(1,54)=6.35$, MSE=129.76, p=.015; active tRNS: 78.86%±SD=15.83; sham tRNS: 66.50%±SD=22.82) but not on Addition and Simple Division, p>.11 (Figure 4). This effect cannot be explained by more trials attempted by the tRNS group (effect of Group or interaction with tasks on the number of trials attempted, p>.18). Rather, this effect was due to increased number of correct responses, shown by an interaction between Group and Task [$F(2,106)=3.99$, p=.030, MSE=3.40, η^2_p=.07; Greenhouse-Geisser corrected]. This interaction was due to the tRNS group solving more

Complex Division problems correctly than those in the sham group [F(1,53)=5.44, MSE=8.73, *p*=.024; tRNS:12.05±SD=4.13; sham:8.91±SD=5.54], which was not the case for Addition or Simple Division problems (*p*>.15).

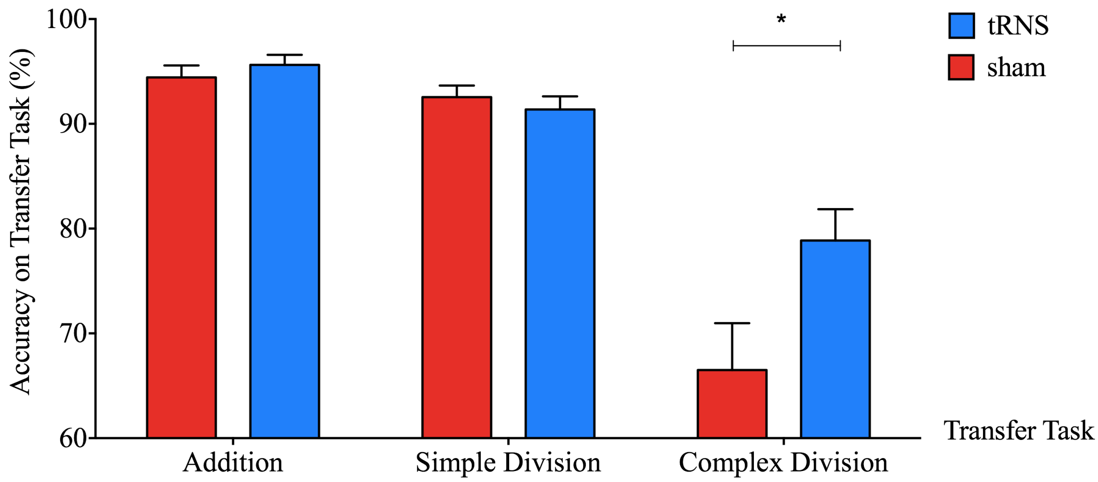


Figure 4 Active tRNS group was more accurate in Complex Division than sham tRNS group when controlled for pre-training performance across tasks.

To assess whether Group difference in Complex Division was linked to training, I performed a partial correlation analysis on training gain [gain in last level=(Day2-Day1)/Day1] and accuracy on Complex Division, controlled for baseline performance (Complex Division at pre-training). I found a significant negative correlation [r=-.372, *p*=.006, 95% CIs (-.61,-.10)], which indicated a *negative* near-transfer effect, whereby higher gains during video game training was associated with a *lower* accuracy in Complex Division after training.

Using a moderation regression analysis, I examined whether this negative transfer was influenced by tRNS during training. Consistent with the correlation findings, training gain was negatively associated with the accuracy in Complex Division post-training (b=-23.44, p=.0002, controlled for accuracy in Complex Division pre-training). However, Group significantly moderated this relationship, as shown by a significant interaction between Group and training gain (b=18.50, p<.037). I decomposed this interaction, and found that the negative relationship between training gain and accuracy in Complex Division occurred only for the sham group (b=-23.44, SE=6.22, p<.0004), but not the tRNS group (b=-4.94, SE=5.78, p>.39).

Working memory

I ran a 2-way ANOVA with Order (Forward, Backward) as the within-subject factor, Group (tRNS, sham) as the between-subject factor, and pre-training scores in both orders as covariates on the standardised scores of Digit Span and Corsi Blocks.

Digit Span I found that the main effects and interactions with Group were not significant (all p>.49)

Corsi Blocks I found an interaction between Order and Group, F(1,54)=5.13, p=.028, MSE=.16, η^2_p=.087). I performed univariate analyses on each forward and backward orders of Corsi Blocks, controlling for the pre-training scores of each order respectively, and found no differences between Groups in each Order, all p>.15.

Questionnaire on side effects

Based on the responses of participants, I did not find any indication of any experienced or perceived severe symptoms that participants attributed to tRNS (see Table 6 below). Instead, I noticed two female participants from the sham group associated tingling sensations below sites of stimulation during training days to tRNS.

Day 1, Post-training

Symptoms	**Sensation**				**Perceived Relevance to tRNS**					**Remarks**
	Absent	Mild	Moderate	Severe	None	Remote	Possible	Probable	Definite	
Headache		1						1^{u}		At the site of stimulation
Neck pain		1			1					
Scalp pain		1				1				Friction with headband
Scalp burns										
Sensations under the electrode (Tingling, itching, burning, pain)		$5^{2\star}$			$1^{1\star}$	1		2^{1u}	1^{u}	
Skin redness		$4^{3\star}$			1	$3^{3\star}$				All- Friction with headband
Sleepiness		$2^{2\star}$				$2^{2\star}$				Looking at the screen and playing the game
Trouble concentrating		$7^{4\star}$	$1^{1\star}$		$7^{4\star}$	1				All - Bored by the game; too long
Change in mood		2	$1^{1\star}$		2	1				All bored with game. 'Remote' - Happy with game feedback
Other		$1^{1\star}$			$1^{1\star}$					Tired eyes

Day 2, Post-training

Symptoms	**Sensation**				**Perceived Relevance to tRNS**					**Remarks**
	Absent	Mild	Moderate	Severe	None	Remote	Possible	Probable	Definite	
Headache		1				1				Due to focusing on the game
Neck pain		1			1					
Scalp pain										
Scalp burns										
Sensations under the electrode (Tingling, itching, burning, pain)		1						1^{u}		Pulsing under stimulation sites
Skin redness		$2^{1\star}$			1	$1^{1\star}$				Friction with headband
Sleepiness		$3^{1\star}$	1		1	2	$1^{1\star}$			Stuffy room
Trouble concentrating		$8^{3\star}$	1	1	$5^{2\star}$	4	$1^{1\star}$			Bored of the game, stuffy room
Change in mood		$2^{3\star}$		1	$2^{2\star}$		$1^{1\star}$			All bored with the game
Other										

Table 6 Responses on side-effects questionnaire. Participants' reported sensation(s) and perceived relevance to tRNS on Days 1 and 2 post-training. Note that ^{x*} marks participants from the tRNS group, where *x* is the number, and ^{u} marks responses by

the same participant. Those from the sham group are the remaining participants, unmarked.

Discussion

In the current double-blind study, I investigated whether applying tRNS during fractions training on a tablet-based video game could further improve learning and performance of older adults compared to training alone. I compared the performance of sham and active tRNS groups on (1) a tablet-based cognitive training that featured mapping fractions on a virtual number line, and (2) near-transfer tasks on Addition, Simple and Complex Division, and far-transfer task on WM. Lastly, I collected and assessed self-rating of physical and cognitive side effects from my participants.

As hypothesized, I found that tRNS further improved training performance; older adults who received active tRNS showed improved accuracy with training, while those who received sham tRNS showed impaired accuracy. Moreover, older adults from the tRNS group were quicker across different levels of fractions mapping, and showed a trend towards achieving higher training levels than the sham group. The latter observation reflects their progression towards more difficult fractions mapping. Together, these findings support the beneficial effects of tRNS on the learning of older adults (Cappelletti et al., 2015). Of interest, tRNS group was not associated with a speed-accuracy trade-off as indicated by sham group's decreased accuracy of mapping with quicker responses across training days. This finding suggests that while the accuracy of the sham group was compromised for quicker responses, improvement in both speed and accuracy in the active group might have been facilitated by the effects of tRNS. One potential explanation is that the application of tRNS mitigated the speed-accuracy trade-off by adding resources available for cognitive processing (Luber, 2014) by means of stochastic resonance (Miniussi et al., 2010; van der Groen & Wenderoth, 2016), whereby 'noise' is added to push neural activity past the threshold for signal detection.

After training, I found that the tRNS group was not linked to a negative transfer effect showed by the sham group. It appears that those in the sham group who achieved higher levels in our game was associated with poorer performance on the Complex Division, thought to share similar mathematical processes. As this was not the case for the active tRNS group, it is possible that tRNS might have mitigated a temporary depletion of shared cognitive resources [previously observed from training alone (Anguera et al., 2012; Persson et al., 2007)] taxed by both fractions mapping and complex divisions. This is not surprising, as training alone on the current game could have been especially cognitively demanding for older adults, given that they were constantly and automatically challenged at their maximal abilities based on their performance. As such, training might have drained resources required for the subsequent Complex Division task, given their shared processes with the cognitive training. Specifically, fractions mapping involved dividing the number line between 0 and 1 according to the size of the fraction's denominator, whereas complex division involved dividing numbers of the same range between 0 and 1. The current observation also supports that of a study on healthy young adults whereby tRNS mitigated task difficulty (Popescu et al., 2016). Finally, given that Complex Division was more difficult than other near-transfer tasks, as evidenced by its lower accuracy (72.9%) compared to Simple Division (91.6%) and Addition (94.9%; all $p<.001$), it might have further exhausted the cognitive resources of older adults thought to be reduced with aging (D. C. Park, 2000; Salthouse, 1988a, 1988b) after training.

Furthermore, I found no immediate adverse physical or cognitive side effects attributed to tRNS based on participants' responses on a questionnaire, which supports its painless and relatively safe application (Fertonani et al., 2015b) for older adults. To this end, current findings suggest that tRNS improved performance without cognitive costs previously reported using tRNS (Cappelletti et al., 2015) and tDCS (Iuculano & Cohen Kadosh, 2013; Sarkar et al., 2014). Differences in findings might have been contributed by mechanisms involved in different tasks, stimulation sites, age and forms of tES (Chaieb, Antal, & Paulus, 2015; Iuculano & Cohen Kadosh, 2013). The underlying mechanisms and factors for such observations, such as the interaction between tRNS and training design with age, require further research. It is also possible that the training improvement and lack of negative transfer of the active tRNS group compared to the sham group might have occurred at cognitive costs that were not detected by the current tasks. Further research should take into consideration that costs and benefits of interventions could appear at different levels [i.e., from molecule to function, (Brem et al., 2014)], or in different forms [e.g., speed-accuracy trade-off in performance, depletion of physical resources, (Kurzban, Duckworth, Kable, & Myers, 2013)].

As the current study was based on behavioural measures, understanding of the underlying biological mechanisms would require integrating physiological methods. For example, multi-modal studies could examine whether current findings were contributed by cognitive and biological factors such as: (1) added resources for neural processing through increasing signal-to-noise ratio via stochastic resonance (Luber, 2014; Miniussi et al., 2010); (2) reduced brain metabolism (Snowball et al., 2013) that might have counteracted depletion of cognitive resources during demanding tasks (Persson et al., 2007); and (3) enhanced “margin” of cognitive reserves (Brem et al., 2014; Stern, 2009) which might have provided greater resources for processing. To conclude, understanding of different levels, from molecule to function (Fertonani & Miniussi, 2016) is needed to understand the mechanisms of cognitive training and tES, and to allow a holistic analysis of the potential costs and benefits of these methods for cognitive enhancement.

Supplemental Methods: Transfer Tasks

Pre-training

Addition task	Simple Division	Complex Division
14 + 38 = ___	2 ÷ 5 =___	70 / 5 =___
29 + 13= ___	6 ÷ 8 =___	92 / 4 =___
56 + 27 = ___	9 ÷ 5 =___	96 / 6 =___
27 + 35= ___	9 ÷ 4 =___	90 / 5 =___
89 + 76 = ___	7 ÷ 25 =___	96 / 12 =___
57 + 68= ___	8 ÷ 32 =___	68 / 17 =___
36 + 79 = ___	3 ÷ 75 =___	90 / 18 =___
85 + 27= ___	6 ÷ 24 =___	78 / 13 =___
254 + 467= ___	27 ÷ 45 =___	222 / 6 =___
689 + 332= ___	54 ÷ 36 = ___	495 / 9 =___
285 + 739 = ___	43 ÷ 50 =___	360 / 8 =___
627 + 496= ___	63 ÷ 12 =___	196 / 7 =___
897 + 253 = ___	84 ÷ 105 =___	276 / 23 =___
176 + 938= ___	69 ÷ 150 =___	731 / 43 =___
956 + 784 = ___	84 ÷ 120 =___	248 / 62 =___
897 + 985= ___	18 ÷ 200 =___	408 / 51 =___
1857 + 1264= ___	126 ÷ 450 =___	762 / 127 =___
1396 + 1915= ___	858 ÷ 130 = ___	448 / 112 =___

Post-training

Addition Task	Simple Division	Complex Division
16 + 36 = ___	3 ÷ 5 =	78 / 6 =___
24 + 18 = ___	4 ÷ 5 =	64 / 4 =___
62 + 29 = ___	7 ÷ 5 =	85 / 5 =___
25 + 37 = ___	2 ÷ 8 =	98 / 7 =___
64 + 77 = ___	6 ÷ 40 =	84 / 14 =___
59 + 83 =___	4 ÷ 80 =	91 / 13 =___
34 + 87 = ___	2 ÷ 25 =	80 / 16 =___
96 + 37 = ___	7 ÷ 28 =	92 / 23 =___
369 + 237 = ___	93 ÷ 12 =	204 / 6 =___
749 + 292= ___	63 ÷ 45 =	294 / 7 =___
743 + 378 = ___	23 ÷ 25 =	424 / 8 =___
628 + 494 = ___	18 ÷ 30 =	207 / 9 =___
885 + 247 = ___	51 ÷ 300 =	703 / 37 =___
183 + 938 = ___	96 ÷ 120 =	234 / 26 =___
968 + 754 = ___	78 ÷ 130 =	372 / 93 =___
976 + 888 = ___	45 ÷ 125 =	702 / 39 =___
1753 + 1368 = ___	825 ÷ 125 =	726 / 121 =___
1473 + 1638 = ___	360 ÷ 500 =	472 / 118 =___

General Discussion

The current thesis is dedicated to extend the research on improving human cognition through the use of cognitive training and tES. Since human cognition is influenced by the variability in the level and rate of learning across populations and individuals, I focused on improving learning in typical and atypical populations, across different age groups. In particular, I examined the use of cognitive training and tES to improve mathematical learning, a cognitive domain with individual variations that has significant individual and societal implications. I chose cognitive training and tES, as these methods are considered safe, accessible, and importantly, shown to produce specific learning gains that are generalisable and long-term, indicators of effective learning. However, the key challenge of both fields lies in their translational research. In particular, the translational potential of both methods is constrained by the use of training tasks that lacked ecological validity. Therefore, I used more realistic training tasks to explore the effects of cognitive training alone (on healthy children), and the combination of cognitive training and tES compared to training alone in typical (healthy adults and elderly) and atypical populations (children with learning disabilities). Through 4 experiments, I examined the following:

1. Would cognitive training alone on a computer-based training improve numerical learning of healthy children? (See Chapter 1)
2. Would combining tES with a video game enhance numerical learning and long-term transfer of healthy adults? (See Chapter 2)
3. Would combining tES with a video game improve numerical learning and transfer of children with mathematical learning disabilities? (See Chapter 3)
4. Would combining tES with an iPad game improve numerical learning and transfer of older adults? (See Chapter 4)

Summary

In the following sections, I will review each of these studies, their limitations (within and between studies), and further work to address them. Before concluding, I will also discuss briefly, the ethics of cognitive enhancement raised by the use of tES.

In **Chapter 1**, I examined whether a computer-based game on mapping number line would improve the numerical learning of typically developing children at school. I chose to train on number line mapping, as it is a relatively straightforward measure of numerical representation that does not require knowledge of measurement units and entities, an ecologically valid task as it is taught formally at school, and performance on this task has been correlated with mathematical achievement (Siegler & Booth, 2004). However, given that correlation and regression studies that used number comparison task (a more common measure of magnitude representation) indicated that the relationship between magnitude representation and mathematical achievement is influenced by the format of representation (i.e., symbolic vs. non-symbolic) [for a review, see (De Smedt et al., 2013)], it is unclear if this might also the case for number line training [which have been based on mapping multiple numerical representations within the same training, for review see (Moeller et al., 2015)]. Therefore in the first chapter, I investigated whether training on mapping Arabic digits vs. dots differentially affects the accuracy and learning of magnitude representation, and the relationship between number line mapping and mathematical achievement. I found that those who trained on mapping digits were more accurate in mapping than those who mapped dots, and showed improved accuracy with training. Compared to correlation and regression studies, the current finding based on training is able to show the impact of training using different formats when learning magnitude representation. Specifically, the current study shows that learning using symbols instead of dots might have promoted more accurate number line mapping and learning through the use of more accurate anchoring strategy. This process might support the refinement of numerical magnitude representation typically observed with schooling, attributed to the acquisition of numerical symbols (Mussolin et al., 2014; Verguts & Fias, 2004). Consistent with previous studies (Siegler & Booth, 2004), I found that mapping accuracy across formats was significantly correlated with mathematical achievement. However, across and within groups, individual mapping accuracy was not linked with mathematical achievement post-training, individual mathematical achievement did not predict later mapping accuracy, and training progress was not related to changes in mathematical achievement.

While the current study demonstrates the impact of format of numerical format on the learning of numerical magnitude, I did not find any transfer effects from this number line training to mathematical achievement, reading abilities or WM capacity. The lack of transfer effects, particularly the relationship between changes in mapping accuracy and improvement in mathematical achievement might be contributed by (1) suboptimal training task design such as the lack of adaptive feature in the current task; and (2) differences in the tasks used for measuring mathematical achievement. In particular, adaptive training has been shown to promote transfer effects compared to non-adaptive training (J. Holmes et al., 2009). Indeed, previous number line studies using identical training design, were adaptive to children's performance have shown transfer to better numerical skills (Käser et al., 2013; Rauscher et al., 2016). Given the specificity of these skills improvement, the current lack of relationship between training progress and changes in mathematical achievement might have been masked by the use of general mathematical achievement test, which might not be particularly sensitive to children's performance changes at this age. Therefore, future studies should consider the use of adaptive training, and measures of achievement that is sensitive to detect changes in a specific population (e.g., curriculum-calibrated tests for children, see Chapter 3). In addition, it has been suggested that greater level of embodiment during training could promote better training outcomes than computerised training alone (Fischer et al., 2011; Link et al., 2013; Moeller et al., 2012). Future studies might also consider the use of active control groups such as those with identical design but with mixed-formats of numerical representation [e.g., those used in (Käser et al., 2013; Rauscher et al., 2016)] to examine effects of constant vs. varied format of training (Vakil & Heled, 2016), and those that train on non-numerical visuospatial skills to examine the specific contribution of training on general visuospatial skills (Simms, Clayton, Cragg, Gilmore, & Johnson, 2016) vs. number line mapping to the acuity and learning of magnitude representation. As I found increased RT with training, which was not attributed to speed-accuracy trade-off, it is unclear whether increased RT might be due motivational or attentional factors. Further studies might incorporate measures (e.g., questionnaires or features integrated in training) to examine such possibilities. Finally, as it is unclear whether the current improvement in training might have cumulative benefits in the long run, further studies on the long-term effects of training specifically on using digits and dots on the acuity of magnitude representation and other cognitive abilities are warranted.

In **Chapter 2**, I designed and used an adaptive video game that involved full-body movements to optimise number line training. I further combined it with tDCS to examine whether the synergistic effects would be greater than training alone in healthy young adults immediately after training and 2 months later. The use of video game is a novelty of this study, as previous tES and training studies within the numerical domain have used simplistic tasks that has little resemblance to those used in the real-world (Cappelletti et al., 2013; Cappelletti et al., 2015; Cohen Kadosh et al., 2010; Popescu et al., 2016; Snowball et al., 2013). I chose to train on mapping fractions, instead of whole numbers, as competence with fractions is a stronger predictor of mathematical achievement than a range of numerical skills, such as whole number arithmetic, number fluency, number line tasks, central executive and intelligence (Bailey et al., 2012; Siegler, Fazio, Bailey, & Zhou, 2013). I found that two days of 30-minute training with active tDCS promoted greater training outcomes (shorter RTs) than sham tDCS with transfer effects, indicated by improved verbal WM capacity. Notably, these effects were specific to the combination of video game and tDCS (but not sham tDCS or the active control group), retained at 2 months follow-up, and appeared to have benefited those with lower baseline in mathematical abilities more than those with higher baselines. Compared to studies within the field of tES and cognitive training, these effects are encouraging, as the training duration is shorter [2 days vs. 5/6 days in tES during training studies (Cappelletti et al., 2013; Cappelletti et al., 2015; Cohen Kadosh et al., 2010; Popescu et al., 2016; Snowball et al., 2013), and up to 100 days in cognitive training studies (Schmiedek et al., 2010)], and transfer effects were found beyond trained domain, which is a rare observation in both fields, with implications for further, translational research. Moreover, I found that the interaction between training and tDCS was differentially modulated by individual differences. Namely, training alone benefited those with higher baseline in mathematical abilities, while combined tDCS and training benefited those with lower baseline. Such findings highlight the need for further research on individual response to the combined use of tDCS and video game, and the potential [or any negative side effects as previously reported (Sarkar et al., 2014)] of this approach for improving cognition and/or reducing cognitive inequalities.

While the behavioural findings are promising, the unique contribution of experimental manipulations (i.e., task features, interaction with tDCS montage) is unclear. Firstly, it remains to be investigated whether the current the observed training gains might also be contributed by improved visuospatial (which involved number line mapping and processing fractions), and/or motor skills given the nature of the current video game (precision in number line dissection through bodily movements) and the montage of right anodal and left cathodal over dlPFC (which might also promote greater visual spatial skills, and motor coordination; see *Chapter 2 Methods* for reasons behind the choice of current montage). Further studies using other a variety of active control groups and montages are needed to disentangle the contribution of these parameters to the current findings. These might include a group that trains on the same task, but without full-body movements to examine the contribution of embodiment during tDCS, a group that also trains on numerical representation but without visuospatial features, such as comparing the size of fractions, and groups that use different montages [left anodal, right cathodal; parietal cortices (PPC) given its involvement in adult numerical processing (Rivera et al., 2005), for discussion on the choice of stimulation of dlPFCs, see section on Further Work below]. Secondly, the factors that contributed to the positive transfer effects observed in verbal WM capacity remains to be understood. Further studies might consider identifying and/or controlling the strategies involved during training, for example by assigning separate groups to train on the same task, with the instructions to use a specific strategy (i.e., verbal vs. visuospatial strategy). In addition, future studies on training using video games might also consider controlling for participants' gaming experience before training. Finally, although the sample size of this study is comparable to those in the published literature and comprised of students from the same university with varied mathematical baseline abilities, it could have benefited from a larger sample size that includes participants from the general population with greater variability in mathematical baseline abilities to increase the power and generalizability of current findings.

In **Chapter 3**, I followed up on the finding that combining tES and video game might benefit those with lower baseline mathematical abilities by examining whether combining tRNS with a professionally gamified version of my video game would improve numerical learning and transfer of children with MLD. This study was aimed at addressing the need for effective, evidence-supported interventions for children with learning disabilities, and empirical evidence to aid the discussion on the use of tES on the developing brain (Cohen Kadosh et al., 2012; Davis, 2014; Maslen, Earp, et al., 2014). Children trained on mapping numbers (digits) instead of fractions, as mapping fractions was beyond their level of competence (based on a pilot session at school). Compared to training alone, I found that active tRNS (but not sham tRNS; only wearing the cap) over bilateral dlPFC during 9 days of cognitive training promoted better training outcomes (more accurate mapping, steeper learning), which translated to better performance on MALT, a diagnostic mathematics test used by the school to monitor children's performance. Note that I used MALT here instead of WIAT, as it is calibrated with the UK curriculum, which might be more sensitive to children's changes in performance (as hypothesized in Chapter 1). These findings support previous studies on healthy adults that tRNS during numerical training promotes better learning and transfer within trained domain (Cappelletti et al., 2013; Cappelletti et al., 2015; Popescu et al., 2016; Snowball et al., 2013), and show that the beneficial effects extend to children with MLD when measured using a real-world task and setting. Furthermore, these results were obtained within a considerably shorter time compared to existing interventions

(9 days vs. weeks to months of consistent training [(Cohen Kadosh et al., 2013; Dowker, 2009)], without any self-reported physical side effects attributed to tRNS.

Compared to my study in Chapter 2 however, I did not find any transfer effects to WM. Differences in these findings might have stemmed from the use of different types of tES (tRNS vs. tDCS; montage, see section on Further Work below), training content (mapping numbers vs. fractions) and its interaction with different populations (children vs. adults; typical vs. atypical populations). Given the scarcity of studies on the use of tES on children, further research is needed to understand the contribution of these factors within this population. Future studies that would involve children with developmental disorders might also consider characterising and controlling for any (potential) comorbidities which are most common in most cases of learning disabilities (Rubinsten & Henik, 2009). These comorbidities are likely to vary across individuals in the type and severity, which are either diagnosed, or exist, but did not meet the criteria for diagnosis. In turn, depending on the condition(s), the training design should be adjusted; for example, if a child with a specific learning disability also has attention deficit hyperactivity disorder (ADHD), the current design of the game, which requires body and hand movements, is likely to be inappropriate and ineffective for training. Hence, it might also be especially useful to investigate the unique contribution of embodiment of the current training to the training gains observed. Finally, it is worth mentioning that at 4-month follow-up assessment, both training groups, with and without tRNS showed sustained improvement on MALT, which suggests that the video game training itself was effective in promoting positive change in children's mathematical performance, which might be a potential intervention for those who are concerned about the use of tES. Given the early-stage challenges in recruitment (Bacchetti, 2013; Bacchetti et al., 2011) and technological development, future studies could ideally include a larger sample size [(Button et al., 2013) especially given the attrition of sample size at follow up encountered in the current study] and adopt a double-blind design to increase the reliability of research findings.

In **Chapter 4**, I extended my investigation on the combined effects of tRNS and video game training to older adults. This study was aimed at addressing the cognitive decline associated with reduced neuroplasticity and cognitive resources, which is increasingly important given the growth and prolonged lifespan of aging population worldwide. I recruited a larger sample (n=61), included additional transfer tasks within the trained domain, and conducted the study in a double-blind fashion compared to my previous studies. Furthermore, the video game used in this study was a gamified version of that used in Chapter 2, which featured fractions mapping. It was further adapted for use on tablet computer (iPad) to increase its usability for older adults (compared to bodily movements using KINECT^{TM} in Chapters 2-3). Older adults trained for 2 days, 30 minutes each (similar to Chapter 2), with active or sham tRNS. I found that active tRNS over bilateral dlPFC throughout training promoted quicker and more accurate performance compared to sham tRNS. These beneficial effects of tRNS mirrored those of my previous studies using tDCS on healthy adults, and tRNS on children with MLD (Chapters 2 and 3) and older adults shown by others (Cappelletti et al., 2015). Crucially, I found that those who received active tRNS did not show speed-accuracy trade-offs during training, and negative transfer effects after training demonstrated by the sham group. It is unclear whether these effects were contributed by fatigue or motivation. Future studies might consider including measures that assess participants' level of attention and motivation during training (e.g., integrated as one of the features of the training), or questionnaire on engagement or fatigue after training. While I did not find any association of physical or cognitive side effects to the use of tRNS based on participants' responses on questionnaire, further studies are needed to understand the mechanisms that prevented these cognitive costs and uncover any negative cognitive or physical costs (Brem et al., 2014; Iuculano & Cohen Kadosh, 2013) that were not detected through the questionnaire approach.

Similar to Chapter 3, I did not find transfer effects to WM capacity. It is difficult to directly compare the findings to those found in Chapter 2, despite training on the same content (mapping fractions), given differences in the modality of response input (finger vs. whole body movement), type of tES used (tRNS vs. tDCS), the stimulation montage (bilateral tRNS vs. Right anodal-Left cathodal tDCS), and age (older vs. younger adults). Further studies are needed to examine whether the observed trade-off and negative transfer effect in the sham group are long-term (or with cumulative effects), and to monitor for potential positive/negative cognitive and physical effects of tRNS in the long run.

It is worth noting that while I investigated the effects of cognitive training and tES across different age groups, it is difficult to directly compare findings across my own studies. This is because I adjusted experimental designs in training and tES parameters depending on the (1) characteristics of the sample population examined in each experiment, (2) situational factors and (3) developments in the literature at the time.

Within the context of cognitive training, there were differences in the tasks used between my studies such as the content, context, duration, mode and environment of training. Specifically, while training in all 4 studies trained on number line mapping, the *content* of mapping differed across groups; typically developing children (Chapter 1) mapped digits and dots within the *context* of numbers between 0-100 on the number line, healthy young (Chapter 2) and older adults (Chapter 4) mapped fractions on adaptive ranges between 0-1, and children with MLD mapped digits (Chapter 3) on adaptive ranges between 0-1500. Such differences in the content and context were adjusted based on participants' abilities (e.g., number, instead of fractions mapping for children with MLD) as well as developments in the literature at the time (e.g., use of adaptive training (J. Holmes et al., 2009; Klingberg, 2010), and fractions as a strong predictor of mathematical achievement (Bailey et al., 2012)). Another difference between the training tasks between chapters is the *design*; in Chapter 1, a cone drops automatically from directly above the location of 50 on the number line and requires a response within about 20 seconds, while in Chapters 2 and 3, the indicator on the number line is varied depending on the initial/previous position of the player's body, and in Chapter 4, the indicator appears on the centre of the line, with no time limit for a response. One direct implication of these differences is that I could not directly compare the pattern and variability of number line mapping across ages (children vs. adults vs. older adults) and between typical and atypical populations (i.e. typically developing children vs. children with MLD). Furthermore, the *duration* of training differed across studies; healthy children trained for 15 days (20 minutes each), young and older adults for 2 days (30 minutes each), while children with MLD trained for 9 days (20 minutes each). Additionally, the *mode* of training for healthy children at school was in groups of 6, while the rest of the studies involved one participant at a time, which in part was due to restrictions of the training *environment.* Specifically, due to the time commitment required (6 weeks of training for two batches of 18 students, everyday) and the number of children involved (n=36), training in groups of 6 was the most practical solution to reduce the amount of interruptions in classroom teaching and learning. Meanwhile, children with MLD trained for 9 days at school after considering the optimal periods available for training within the particular term timetable, and agreed commitment from teachers.

Within the context of tES, there were differences in the parameters used between my studies such as the type, montage, dosage, duration and number of sessions of tES. Specifically, I used tDCS in Chapter 2, but following the development of literature at the time that showed comparatively better learning with tRNS than tDCS in another cognitive domain (Fertonani et al., 2011), I explored the effects of tRNS in Chapters 3 and 4. The use different types of tES also contributed to differences in the stimulation montage used during training, as tRNS was polarity-independent (anodal on both right and left dlPFC) unlike tDCS (anodal and cathodal on either side). Furthermore, I applied a lower dosage of tRNS on children with MLD, which was 75% of that applied on young and older adults in my own studies and those in the literature (1mA) having considered differences between these populations such as head size and scalp thickness (Kessler et al., 2013; Opitz et al., 2015). Finally, the duration and number of sessions of tES varied between children with MLD (9 sessions, 20 minutes each) and those of young and older adults (2 sessions, 30 minutes each) given the training design (having adjusted for the experimental setting and commitment from participants involved).

More generally, given practical limitations, I did not conduct long-term follow up on the studies presented at Chapters 1 and 4, or collect physiological data from my participants. Nonetheless, my studies support those of the current literature that cognitive training modulates learning and performance (Chapters 1- 4), and training outcomes could be enhanced using tES (Chapters 2-4). Moreover, my findings extend on the literature to show that training effects are influenced by training content (training on dots vs. digits: Chapter 1), stimulation parameters (tDCS vs. tRNS: Chapters 2-4) and individual differences (lower vs. higher cognitive baselines: Chapter 2; age: Chapters 2-4), and highlight the need for understanding the underlying mechanisms. Ideally, systematic understanding of each of these unique contributions and their mechanisms of action would allow better design and evaluation of training and stimulation outcomes, given the desired effects for a target population, and eventually, for individuals.

Further Work

While many have asked, does training and tES work, or does it not? Perhaps, the question could be rephrased: how could we make training and tES work better? In this section, I outline further work that could *optimise* the experimental design, and evaluation of findings of (1) training and transfer tasks, and (2) tES parameters, with emphasis on the consideration of (3) individual differences and (4) underlying mechanisms.

1. Training and transfer tasks

As highlighted by the current studies (e.g., Chapter 1 vs. Chapters 2-4) and others (as reviewed in this paragraph), training and transfer outcomes are influenced by tasks used in training and assessing transfer. When designing training tasks and evaluating training effects, depending on the desired outcomes, future studies should consider investigating the impact of training or task features such as content [e.g., context of number line mapping, 0-100 vs. 0-1000 (Siegler & Opfer, 2003); the different components involved [e.g., in arithmetic (Dowker, 2005; W. Holmes & Dowker, 2013)], difficulty level (K. T. Jones & Berryhill, 2012), adaptive vs. non-adaptive versions (J. Holmes et al., 2009), basis of adaptive features [i.e., adjustment based on RT, conceptual difficulties (Obersteiner et al., 2013), accuracy level (%), or maintaining a certain level of performance, e.g., at 75% (Kuhn & Holling, 2014) or 80% (Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger, Gälli, et al., 2011)], type of feedback [e.g., 3D representation of the number line (Chapter 1) vs. multi-representation of the number line location (Chapter 2) vs. direct location on the number line (Chapters 2-4); overall performance through display of progress on the screen], mode of training [e.g., in groups or one-on-one, with or without the attention of the experimenter, the 'observer-expectancy' effect (Rosenthal, 1966)], training environment (e.g., school vs. laboratory), instruction (e.g., to map number on the number line vs. to identify the numerical value on a specific location on the number line), type or extent of embodiment involved in training (e.g., whole body vs. finger movements), motivational elements (Katz, Jaeggi, Buschkuehl, Stegman, & Shah, 2014), medium of presentation (pen-and paper, computer-based, tablet-based, virtual reality) and response [KINECT™, touch-screen, joystick (Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger, Gälli, et al., 2011; Link et al., 2013)], duration (per session, and overall training period), timing (i.e., interleaved vs. consecutive training) (Wang, Zhou, & Shah, 2014), approach [e.g., process based vs. general skills (Jolles & Crone, 2012)] of training [for more factors to consider, see (Green et al., 2014)].

As for transfer tasks, the design (or choice) and the effects measured should consider potential near- and/or far-transfer effects [as assessed in Chapter 4 (Melby-Lervåg & Hulme, 2013)], specificity of training effects [e.g., general vs. components of mathematical skills, (Vanbinst et al., 2012)], and quantity and quality of questions (to avoid ceiling effects in performance on certain tasks, see Chapter 4) to ensure that transfer task(s) are relevant and sensitive enough to detect and reveal transfer effects (as proposed in Chapter 1). Importantly, to examine the relevance of training effects in real-life, studies should adopt tasks that measure everyday cognition [e.g., (Strenziok et al., 2014)] or real-world measures used in educational (Chapter 3) or clinical settings (van Heugten et al., 2016).

Of relevance to both training and transfer tasks, further research should also compare, contrast and consider the sensitivity and representation of different types of indices (e.g., RT, accuracy: percent absolute error, number of correct, ratio between stimuli) used to in defining performance on a single cognitive component or construct, within the same and across different studies [for a review on measures used to index numerical magnitude representation, see (Dietrich et al., 2016)]. Finally, design and evaluation of training and transfer tasks could be optimised based on individual differences (see the following section, 3. Individual differences), and underlying mechanisms (see the following section, 4. Underlying mechanisms).

2. tES parameters

As indicated by the current studies (Chapters 2-4) and others (as reviewed in this paragraph), training and transfer outcomes are likely to differ according to the type (e.g., tDCS and tRNS) and parameters of tES used. Currently, most tES studies on cognitive enhancement within and beyond the numerical domain are based on tDCS [for a review, see (Looi & Cohen Kadosh, 2014)], with few using tRNS [e.g., for a review on the numerical domain, (Looi & Cohen Kadosh, 2016)]. Given that no studies within the numerical domain to my knowledge have directly compared the effects of tDCS vs. tRNS, future studies could examine the effects of different types of tES on the same training and population.

In terms of tES parameters, stimulation site(s) are of particular importance to training studies, as these cortical regions might be differentially engaged during training, which might result in training and transfer outcomes. In the current thesis, I have focused on the dlPFCs, which present both potential benefits and limitations. While the benefit might be potentially greater transfer effects given the vast overlap of neural network and hence, executive functions (Diamond, 2013) subserved by these regions, the limitation would be the difficulty in pinning down the specific cognitive mechanism(s) that were enhanced or contributed to the observed effects. Therefore, further studies with varied transfer tasks that tap on the varied executive functions are needed to disentangle effects related to stimulation of the dlPFC. Within the numerical domain, other stimulation sites that could be of potential interest are the PPCs (Rivera et al., 2005), although these regions are also associated with visuospatial perception, spatial attention and a range of other functions (Constantinidis, Bucci, & Rugg, 2013). Depending on the theory in mind, and task (training and goal) at hand, future studies could compare the effects of different sites (dlPFC vs. PPCs), montages (RA-LC vs. LC-RA) of these sites [e.g., (Iuculano & Cohen Kadosh, 2013)], and even simultaneous stimulation of PPCs and dlPFCs, and its interaction with task difficulty (Popescu et al., 2016). Studies could also examine the impact of stimulation montage such as bilateral vs. unilateral (with the return electrode placed over the contralateral site vs. extracephalic regions, e.g., shoulder, and size (Bikson et al., 2010), type of electrodes used [e.g., EEG electrodes, (Marshall, Molle, Hallschmid, & Born, 2004) vs. sponge electrodes], spacing between electrodes (Bikson et al., 2010; Moliadze, Antal, & Paulus, 2010), shape, size and arrangement of sponges used (Datta et al., 2009; Miranda et al., 2013; J. H. Park, Hong, Kim, Suh, & Im, 2011) and high-definition (HD) stimulation (Gbadeyan, Steinhauser, McMahon, & Meinzer, 2016) on training effects. In addition, systematic investigations and optimisation of the effect of stimulation dosage (Boggio et al., 2006; Hoy et al., 2013; Iyer et al., 2005), intensity (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013), duration (Ohn et al., 2008), timing [before vs. during vs. after stimulation, (Javadi, Cheng, & Walsh, 2012)] (Martin, Liu, Alonzo, Green, & Loo, 2014; Tremblay et al., 2016) [e.g., interleaved vs. consecutive, (Alonzo et al., 2012; Lin et al., 2011); inter-stimulation interval (Monte-Silva, Kuo, Liebetanz, Paulus, & Nitsche, 2010)] given a specific training within a specific population are needed. Meanwhile, novel methods to improve the reliability and effectiveness of tES, and its importance has been demonstrated by the patents filed between 2010 and 2015 (Malavera, Vasquez, & Fregni, 2015).

3. Individual differences

As highlighted in Chapter 2, the effects of training alone vs. training with tES were modulated differently by individual differences in baseline abilities. Given individual differences in behaviour, cognition and genetics, as well as variability in the reported effects of and responses to cognitive training (Jaeggi et al., 2014) and tES (Krause & Cohen Kadosh, 2014; Wiethoff et al., 2014), inter-individual factors should be taken into consideration when optimising training, transfer tasks and tES parameters, and when evaluating the resulting effects.

When designing and evaluating cognitive training, factors such as age (Brehmer et al., 2012; Double & Birney, 2016; Jolles & Crone, 2012; von Bastian & Oberauer, 2014; Zinke et al., 2014), participant motivation, need for cognition, implicit theories about intelligence, baseline abilities (Jaeggi et al., 2014) in specific components trained (Dowker, 2005), temperament (Studer-Luethi, Bauer, & Perrig, 2016), strategy use (Lee et al., 2015), expectation (Foroughi, Monfort, Paczynski, McKnight, & Greenwood, 2016; Green et al., 2014), personality and genetic factors [for a review, see (von Bastian & Oberauer, 2014)] should be taken into account.

Meanwhile, when considering tES parameters, the following factors might be relevant: inter-individual variation in head fat (Truong, Magerowski, Blackburn, Bikson, & Alonso-Alonso, 2013), head size (Kessler et al., 2013), anatomical differences, individual brain state (L. M. Li, Uehara, & Hanakawa, 2015), and cortical region(s) targeted [some which are more heavily influenced by genetics, e.g., dlPFC (Kanai & Rees, 2011)]. When interpreting effects, it is worth considering the impact of individual differences in educational level (Berryhill & Jones, 2012), personality (Pena-Gomez, Vidal-Piñeiro, Clemente, Pascual-Leone, & Bartrés-Faz, 2011) individual traits (Sarkar et al., 2014), age (Cappelletti et al., 2015), baseline performance (London & Slagter, 2015; Looi et al., 2016), experience with tES [e.g., naïve vs. experienced participant (Ambrus et al., 2010)] and response to varying current intensities (Chew, Ho, & Loo, 2015) [for are comprehensive review, see (Krause & Cohen Kadosh, 2014)]. Finally, more work is needed to establish the reliability and consistency of tES response at the intra-individual level (Dyke, Kim, Jackson, & Jackson, 2016).

Understanding the interactions between these inter-variable factors and cognitive training alone, with tES, and tES alone could contribute towards understanding individual responses (positive and negative) to such interventions and eventually development of customised application (Mishra, Anguera, & Gazzaley, 2016), similar to the approach of personalised medicine (Santarnecchi et al., 2015).

4. Underlying mechanisms

While my own studies might have hinted at cognitive mechanisms underlying the effects of cognitive with and without tES, the neurobiological mechanisms of these methods remain unknown, similar to most studies in both fields. Understanding the mechanisms of training and those that support transfer effects could guide optimisation of training, transfer tasks and tES parameters.

Within the field of cognitive training, most of the studies on mechanisms have been focused within the WM domain [for reviews, see (Constantinidis & Klingberg, 2016; Klingberg, 2016)]. While these studies have contributed important insights to the development of experimental designs that promote training and transfer (Dahlin et al., 2008; Olesen et al., 2004), the neural mechanisms of training and transfer is likely to differ to some extent, depending on the cognitive domain(s) involved, individual differences such as strategy use, the specific training task, population and the individual. To examine the specificity of such effects, future studies could combine real-time, task-based neurofeedback during training. This would allow individuals to adjust their performance or strategy depending on both online feedback on their behavioural performance and their brain activity using portable technologies such as EEG or fNIRS (Hosseini, Pritchard-Berman, Sosa, Ceja, & Kesler, 2016) [for a review on such multi-modal approaches, see (Mishra et al., 2016)].

Within the tES field, understanding the underlying mechanisms is a priority, given increased scrutiny of reported effects from within and outside the field (Soekadar et al., 2013). The lack of knowledge on the underlying neurobiological mechanisms of "online" and "offline" tES effects impedes the understanding of short- and long-term effects (positive and negative) that is important to prevent social and health risks (Dubljević, 2015). Specifically, understanding such mechanisms could shed light on (1) where, how and when to optimise the effects of stimulation (Bergmann, Karabanov, Hartwigsen, Thielscher, & Siebner, 2016); (2) tolerability and potential cumulative effects of prolonged use (Paneri et al., 2016); (3) interaction with drugs targeted to the central nervous system (Boggio et al., 2010; Brunoni, Ferrucci, et al., 2013) to not prevent the use of tES by those with conditions that rely medication(s); and (4) interaction with neurodevelopment, which might be especially important within the context of developmental disorders when deciding on the optimal age of intervention, and in examining the developmental neuropathology (Oberman & Enticott, 2015).

Therefore, more research that adopts computational modelling (Bestmann et al., 2015; Bonaiuto & Bestmann, 2015) and multi-modal approaches, i.e., combining tES with neuroimaging methods (Dayan et al., 2013) such as fMRI (Alekseichuk, Diers, Paulus, & Antal, 2016; Hauser et al., 2016; Tate et al., 2016)], magneto-encephalography [(MEG) (Hanley, Singh, & McGonigle, 2015)], fNIRS [(Ehlis, Haeussinger, Gastel, Fallgatter, & Plewnia, 2016; McKendrick, Parasuraman, & Ayaz, 2015; Snowball et al., 2013)] and EEG [(Anguera et al., 2013; Mancini et al., 2016)] is warranted [for review, see (Soekadar, Herring, & McGonigle, 2016)] to delineate and understand the multi-level effects (Bestmann et al., 2015; Fertonani & Miniussi, 2016). In particular, the use of tES with mobile imaging technology could be advantageous for experimentation (and eventually application) in natural settings [e.g., fNIRS (McKendrick et al., 2015)].

In general, the fields of cognitive training and tES could both benefit from studies involving larger sample sizes (Brunoni et al., 2012) to reduce type 1 and 2 errors in statistical interpretations, long-term follow ups to examine for long-term effects which might surface later (Floel et al., 2012; Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger, Gälli, et al., 2011)[or for tES, after repeated use (Paneri et al., 2016)], that control for placebo effects (Foroughi et al., 2016), double-blinded randomised controlled trials, replications by other labs on the same regimes to examine the reliability and generalizability of studies (Looi & Cohen Kadosh, 2016), and pre-registration of studies (Gonzales & Cunningham, 2015) to reduce publication bias, or the 'file drawer' effect (Rosenthal, 1979) and increase research integrity, which might be especially relevant for studies that might be faced with conflicts of interest (Rabipour & Raz, 2012; van Heugten et al., 2016).

As outlined above, much experimental work is needed to establish the reliability and effectiveness of cognitive training and tES in improving learning and cognition. It is worth noting that while research has stimulated new knowledge and potential applications, it has also stimulated important ethical debates, especially in the case of tES.

Ethics of tES for cognitive enhancement

Of particular relevance to the current thesis are the ethics concerning the use of tES for healthy adults (Hamilton et al., 2011), and children (Cohen Kadosh et al., 2012; Davis, 2014). The key concern in both cases is the issue of safety. Other issues include character, justice and autonomy (Farah et al., 2004; Greely et al., 2008; Hamilton et al., 2011), which I will discuss briefly.

On the subject of safety, although tES appear to be safe when used within recommended guidelines in adults (Bikson et al., 2016; Fertonani et al., 2015b) and children (Krishnan, Santos, Peterson, & Ehinger, 2015; Moliadze et al., 2015; Palm et al., 2016), the concern of safety remains given the lack of mechanistic understanding of effects and side effects [in adults (Bestmann et al., 2015; Fertonani & Miniussi, 2016) and children (Davis, 2014)], potential health and social risks (Dubljević, 2015), and general lack of data, especially in the case of children (Krishnan et al., 2015; Palm et al., 2016). The issue of safety is exacerbated by the unregulated access of tES devices over the Internet, unfounded claims about its effects, misrepresentation by the media, growth of do-it-yourself (DIY) community (Fitz & Reiner, 2013; Riggall et al., 2015).

Given findings of improved cognitive performance at the impairment of another in adults (Iuculano & Cohen Kadosh, 2013; Sarkar et al., 2014), the cost-to-benefit ratio of this application has been questioned (Brem et al., 2014), especially for healthy populations who might not necessarily need such enhancement [or "cosmetic neurology" (Hamilton et al., 2011; Lapenta, Valasek, Brunoni, & Boggio, 2014)] and vulnerable populations, such as children who are not in the position to make such decisions (Cohen Kadosh et al., 2012; Maslen, Earp, et al., 2014). In the latter case, the prevailing concern is the interaction between the developing brain and the incalculable stimulation effects; while accelerated neural plasticity of the younger brain might offer enhanced potential for mitigating neural atypicalities, there is a risk that it might also amplify potential harmful effects, especially without systematically defined stimulation protocols (Davis, 2014; Fitz & Reiner, 2014; Palm et al., 2016). While this is a considerable concern, so is the deprivation of a considerable population of children with neurodevelopmental conditions from potentially improved cognition and life outcomes [(Cohen Kadosh et al., 2012), as addressed in Chapter 3]. Indeed, it has been proposed that the cost-benefit analyses of tES application would differ depending on enhancement or treatment (Maslen, Earp, et al., 2014), and alternatives, e.g., caffeine (Dresler, 2013; McIntire, McKinley, Nelson, & Goodyear, 2016) available to each specific condition. The current consensus is that there are no ethical reasons against the use of tES in children in the case of medical conditions that compromises the child's wellbeing, especially in the absence of a reasonable alternative (Palm et al., 2016), but tES is not recommended for enhancement purposes in healthy, typically developing children (Maslen, Earp, et al., 2014; Palm et al., 2016).

As for the potential use of tES for cognitive enhancement for healthy, typical populations, it has triggered concerns about social risks on aspects of human character, justice and autonomy. On the subject of *character*, some have highlighted the potential threat of tES enhancement to an individual's identity, traits, sense of authenticity and meaning of human life in all its imperfections, and fears about risks of commodifying and potentially eroding our appreciation of such characteristics (Farah et al., 2004; Hamilton et al., 2011). In short, are we willing to change our fundamental nature, for the 'better versions' of ourselves? On the subject of *justice*, some have asked, would the use of tES be considered as 'unfair advantage' or cheating? Would it be accessible to individuals from all socio-economic backgrounds? Would it widen the gap between those with higher and lower baseline cognitive abilities? (As addressed in Chapter 2) Finally, on the subject of *autonomy*, if tES were approved for personal use, should individuals such as those with neurodevelopmental disorders or high-duty professionals be explicitly coerced to use tES for cognitive enhancement against their will? Would typical populations be implicitly coerced to remain employed or for the sake of career promotion? (Lapenta et al., 2014) As illustrated by these questions, there are considerable amount of issues pertaining to, but are not specific to the potential use of tES for cognitive enhancement (Farah et al., 2004; Greely et al., 2008; Hamilton et al., 2011; Lapenta et al., 2014).

To date, the research community has responded to some of these ethical issues, with focus on the subject of safety by what I would summarise as the 3Rs: Research, Report and Regulate. Notably, researchers have repeated emphasised the need for more research on the mechanisms of tES in the short- and long-term (Bestmann et al., 2015; Dubljević, 2015; Fertonani & Miniussi, 2016). With regards to studies involving children, experiments with carefully planned protocols with well-characterised samples, systematic and long-term monitoring of effects and side-effects, with serious ethical considerations for each treatment have been strongly recommended [(Cohen Kadosh et al., 2012; Croarkin & Rotenberg, 2016; Davis, 2014; Palm et al., 2016), as been taken into account in Chapter 3]. In terms of reporting, some have highlighted the importance of responsible communication of research findings within the research community (e.g., reporting null and/or negative findings or side-effects, as reported in Chapter 4) and to the wider audience (e.g., informing the plausibility of effects, emphasizing the potential side effects and limitations of research (Cabrera & Reiner, 2015; Davis, 2014; Davis & Koningsbruggen, 2013; Dubljević, 2015; Hamilton et al., 2011) to reduce and prevent misunderstanding, misuse and abuse. Finally, tES researchers have teamed with bioethicists in proposing various frameworks (De Ridder, Vanneste, & Focquaert, 2014; Dubljević, 2015; Fitz & Reiner, 2013; Fregni et al., 2015; Maslen, Douglas, Cohen Kadosh, Levy, & Savulescu, 2014) to regulate the access and use of tES to protect public interests and safety.

Conclusion

The current thesis demonstrates that cognitive training and tES could improve learning and cognition of typical and atypical populations across different age groups, as modelled using the numerical domain. My studies highlight the role of content in training outcomes (Chapter 1), and that the use of tES could further enhance training and transfer effects from cognitive training alone (Chapters 2-4). Furthermore, they show that the combined approach of tES and cognitive training could have long-term positive effects that benefit those with lower baseline cognitive abilities (Chapter 2), effects that are meaningful to the real-world (Chapter 3) and the possibility of mitigating cognitive trade-offs from training alone (Chapter 4). Further research that optimises the design of training and transfer tasks, and tES parameters, with the consideration of individual differences and underlying mechanisms are needed to improve training and transfer outcomes. Considering the ethical concerns raised by the use of tES for cognitive enhancement, it is clear that both scientific research and bioethical discussions are needed to guide future directions on improving learning and cognition of the individual and for all.

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