Neurobiology of Learning and Memory 133 (2016) 7–12

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Transcranial random noise stimulation benefits arithmetic skills

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ARTICLE INFO

Article history:
Received 8 December 2015
Revised 9 May 2016
Accepted 14 May 2016
Available online 17 May 2016

Keywords:
Frontal cortex
Parietal cortex
Transcranial random noise stimulation
Arithmetic competence
Dyscalculia
Acalculia

ABSTRACT

Although arithmetic skills are crucial cognitive abilities, numeric competence impairments affect a significant portion of the young population. These problems produce a high socio-economic cost by negatively affecting scholastic and work performance. The parietal cortex is the brain area that is classically associated with numeric processing, *but* it is still debated whether other cortical areas are involved, and only a few studies tried to directly assess the *causal* link between brain and this cognitive function by using transcranial random noise stimulation, tRNS. This non-invasive electric stimulation device has been shown to enhance activity in the underlying cortex. We tested three groups of participants with equivalent arithmetic skills – an arithmetic 'screening' was administered. One group was stimulated by tRNS on the frontal lobe, another on the parietal lobe, and a third group was assigned to the placebo condition. During the stimulation, participants performed a subtraction verification task. To investigate long-term effects of tRNS, the task was repeated seven days later without stimulation. Aside previously-tested (familiar) subtractions, in the second experimental session unfamiliar subtractions were also administered. We found that, compared to placebo, parietal and frontal stimulation significantly reduced reaction times immediately, and enhanced accuracy after seven days. This benefit encompassed both familiar and unfamiliar subtractions. These results suggest that modulation of frontal and parietal cortices may ameliorate basic arithmetic skills by benefitting working memory function. This could open new avenues for neuro-restorative applications of brain stimulation.

1. Introduction

Numeric and arithmetic competencies are important cognitive functions that can be impaired in young and adult population (Butterworth, Varma, & Laurillard, 2011; Von Aster & Shalev, 2007; Willmes, 2008). Numeric ability decay is particularly debilitating when it involves basic calculation skills, such as addition and subtraction, because they are normally used on a daily basis. The loss or impairment of numeric competence due to aging, brain lesions, and neuronal degeneration negatively affects academic and work performance, and contributes to impoverishment of the 'cognitive capital' of a nation (Beddington et al., 2008).

It is generally believed that the brain areas involved in numeric cognition are located within the *parietal* lobe (Anderson, Damasio, & Damasio, 1990; Bueti & Walsh, 2009; Cohen Kadosh & Walsh, 2009; Mussolin, Mejias, & Noël, 2010), but a minority of studies suggest that the *frontal* lobe might also be involved in numeric cognition (Arsalidou & Taylor, 2011; Capone et al., 2014; Galfano, Penolazzi, Vervaeck, Angrilli, & Umiltà, 2009). Thus, there is still disagreement on the cortical areas supporting numeric cognition and we will investigate this issue. Only a handful of studies (e.g. Snowball et al., 2013) attempted to clarify this point by *directly* determining the *causal* role of cortical areas (other than the parietal cortex) in numeric cognition by using transcranial random noise stimulation (tRNS). Brain stimulation is a method to determine whether cortical regions are causally related to a particular cognitive function, rather than mere correlating cortical activity and functions (Penolazzi, Stramaccia, Braga, Mondini, & Galfano, 2014).

Among brain stimulation techniques, tRNS is a relatively novel method delivering random alternating currents to the brain cortex that can produce enduring effects (Fertonani, Pirulli, & Miniussi, 2011; Terney, Chaieb, Moliadze, Antal, & Paulus, 2008). Although the explanation of the underlying mechanism is rather speculative, tRNS enhances neural activity by acting on sodium channels (Na^{+}), which might support the long-term effect of tRNS (Paulus, 2011; Terney et al., 2008). As we were interested into the long-term benefit of brain stimulation then we chose tRNS. Additionally, tRNS was chosen because it presents an advantage over other brain stimulation techniques, such as transcranial direct current stimulation (tDCS). In fact, tRNS is unlikely to produce 'burning' or 'itchy'

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http://dx.doi.org/10.1016/j.nlm.2016.05.004
1074-7427/

sensations, headache, redness, or to be detected (Ambrus, Paulus, & Antal, 2010; Fertonani, Ferrari, & Miniussi, 2015).

Within the parietal and frontal lobes we stimulated the areas that are likely to support numeric cognition, such as the dorsolateral prefrontal cortex (DLPFC, Arsalidou & Taylor, 2011; Zamarian, Ischebeck, & Delazer, 2009) and the posterior parietal cortex (PPC, Cohen Kadosh, Soskic, Iuculano, Kanai, & Walsh, 2010). A placebo/sham condition was also included. As mentioned above, the parietal cortex (and PPC) is traditionally considered to support numeric cognition (Anderson et al., 1990; Bueti & Walsh, 2009; Cohen Kadosh & Walsh, 2009) *rather* than frontal cortex. However, also the frontal cortex (and DLPFC) has been found to support numeric cognition (Arsalidou & Taylor, 2011; Snowball et al., 2013; Zamarian et al., 2009). Are both areas involved in this task? This is what we will investigate. These seemingly odd findings may be due to the fact that DLPFC and PPC support working memory function (Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011; Ohn et al., 2008; Wu et al., 2014). Working memory is defined as the cognitive 'space' in which information is briefly stored *and* processed (Baddeley, 2000; Baddeley & Hitch, 1974). As mental arithmetic computation involves both storing and manipulating information, since the early days of experimental psychology it was believed to be a 'typical' task performed by working memory (Hitch, 1978). Nowadays, this hypothesis has been confirmed by numerous studies (Hecht, 2002; Imbo, Vandierendonck, & Vergauwe, 2007; Logie, Gilhooly, & Wynn, 1994). Thus, by using tRNS, in our study we targeted the brain areas supporting working memory (DLPFC and PPC) to investigate which one is *the most* involved in arithmetic computation.

Due to its high socio-economic relevance (Butterworth et al., 2011), our task involved one of the basic arithmetic operations, namely subtraction. Participants were stimulated while they performed a subtraction verification task. Additionally, we were interested in any long-term effect of tRNS (Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Snowball et al., 2013), therefore participants' arithmetic task was performed both during the stimulation and seven days later (without stimulation). A long-term positive effect of the stimulation would suggest that this technique has the potential for long-lasting neuro-rehabilitation. Another methodological feature is that after the seven-day period, participants performed the subtraction verification task on the same set of subtractions as in the first session ('old' subtractions) and on a 'new' set of subtractions. The aim of this procedure was to investigate whether any positive effect of tRNS was limited to the previously presented material (old subtractions) or whether the benefit extended beyond to new material (new subtractions). Verifying the latter case would suggest that, rather than simply improving the memory for previously presented material (old subtractions), tRNS improved the ability of working memory of performing subtractions. This result would have broader implications for neural rehabilitation.

Based on previous studies using this type of brain stimulation (Snowball et al., 2013) we expected to find that, compared to sham stimulation, tRNS on either the frontal or the parietal cortex would produce immediate and long-term benefit to the arithmetic task; we remain agnostic about the effect of tRNS on newly presented material (new subtractions).

2. Material and methods

2.1. Participants

Fifty-four participants (27 males and 27 females) were recruited among the students of Sabanci University. Before being accepted for the study, each participant completed an exclusion questionnaire ensuring that none of them was affected or had history of neurologic, psychiatric, or systemic pathologies incompatible with brain stimulation (e.g. epilepsy); had history of substance abuse; was under any drug treatment acting on the central nervous system; was affected by motor impairments; or had damaged skin over the scalp. Every participant had normal or corrected-to-normal vision, and signed the consent form approved by Sabanci University Research Ethics Committee. Each experimental group was composed of 18 participants (nine males and nine females). The group that was frontally stimulated had an average age of 21.2 (SD = 3.1) years, the parietal group had an average age of 21.3 (SD = 2.6) years, and the sham group had an average age of 22.0 (SD = 4.4) years.

2.2. Apparatus and procedure

Participants were tested in two different experimental sessions with a 7-day gap in-between. In the first session, participants filled the above-mentioned exclusion questionnaire, signed the consent form, run a paper-and-pencil test to assess their arithmetic skills, had the two electrodes placed on their heads (for both verum and sham stimulation), and completed the subtraction verification task. In the second session participants were tested on the same set of subtractions they verified seven days before, intermixed with a new set of subtractions; here *no* brain stimulation was provided.

During the first session, before using tRNS participants received a sheet with 20 arithmetic problems to solve (multiplications, additions, subtractions, and divisions, see Supplementary material). They had two minutes to solve as many problems as possible. This procedure was aimed to detect any pre-existing differences across groups. Then participants were randomly assigned to one of the three experimental groups; for the groups receiving verum stimulation (i.e. not for the placebo group) tRNS was bilaterally delivered by a DC Stimulator Plus™ device (neuroConn GmbH, Germany) through two 5×5 cm electrodes inserted into saline-soaked synthetic sponges. Stimulation consisted of high frequency noise (100–600 Hz) with an intensity of 1 mA. The frontal and parietal groups received 20-min stimulation with increasing/decreasing 'ramps' of 10 s at the beginning and at the end. Following an established methodology (Cohen Kadosh et al., 2010; Terney et al., 2008), participants of the sham (placebo) group had electrodes on their heads for 20 min, but stimulation lasted 20 s only. More specifically, participants in the frontal group were bilaterally stimulated placing the electrodes on F3 and F4 of the International 10–20 system used for EEG studies (Homan, Herman, & Purdy, 1987[1]), those of the parietal group received bilateral stimulation on P3 and P4, and those in the sham group received bilateral 'placebo stimulation' on either F3–F4 or P3–P4. A double-blind procedure was adopted; participants were not aware of the type of stimulation and a naïve research assistant ran the entire experimental session. With an excuse, the experimenter was called to the lab to *activate* the tRNS equipment (either verum or sham); the experimenter was in the lab for far less than one minute.

Stimuli consisted of 24 subtractions, 12 displaying correct results (e.g. $73 - 58 = 15$) and 12 displaying wrong results (e.g. $64 - 48 = 14$). Sixteen subtractions required 'borrowing', and eight did not (equally distributed across 'correct' and 'wrong' subtractions). An additional set of 12 'new' subtractions (six correct and six wrong) was used in the second experimental session occurring seven days later. These subtractions were intermixed with 12 of the 'old' subtractions; for both old and new subtractions seven required borrowing and five did not (see Supplementary materials, Table S1).

[1] We measured the head of each participant along the two main axes (left–right from the auditory canals, and front–back nasion to inion), and calculated the coordinates for the DLPFC and PPC.

While they were stimulated, in the first session participants performed four blocks of the subtraction verification task where they judged the correctness of the subtraction results that appeared on the computer screen. E-Prime™ (Psychology Software Tools Inc., USA) was used to display the stimuli and collect responses. Each subtraction was sequentially displayed for a maximal duration five seconds. Feedback on the answers was not provided. Each block lasted around two minutes. Participants were required to be as fast *and* as accurate as possible. To keep participants focused by varying the task, after each block there was an unrelated distractor task (word categorisation[2]) which lasted for about two minutes.

In the second experimental session, occurring seven days later, participants performed the subtraction verification task where old subtractions, upon which they were tested seven days before, were intermixed with new subtractions (word categorisation was also performed). The first experimental session took about 30 min, while the second session lasted less than 10 min.

3. Results

First of all, we analysed the performance in the paper-and-pencil arithmetic test by running a one-way ANOVA on the number of correctly solved arithmetic problems. The independent variable was the Group to which participants were later assigned (frontal, parietal, or sham). We found null results [$F(2,51) = 0.05$, $p = 0.95$] suggesting that there was not any significant difference in arithmetic skills across the three groups; on average participants assigned to the frontal group correctly solved 8.6 arithmetic problems (SD = 2.5), those assigned to the parietal group 8.9 (2.6), and those assigned to the sham group 8.7 (2.6).

Secondly, we verified whether the type of stimulation affected the arithmetic performance in the first session (first day). Thus, we ran a two-way ANOVA on the percentage of correct responses (i.e. the subtraction results that were correctly judged as correct/wrong) with Stimulation (frontal, parietal, or sham) and Block (1st, 2nd, 3rd, or 4th) as independent variables. The effect of Stimulation was not significant [$F(2,51) = 2.47$, $p = 0.10$], while that of Block was significant [$F(3,50) = 3.27$, $p = 0.02$], indicating that, as blocks proceeded, participants became more accurate in their responses. The interaction Stimulation by Block was not significant [$F(6,47) = 0.29$, $p = 0.94$] (see Table 1). We performed the same analyses on the reaction times for correct trials, and found that the effect of Stimulation was marginally significant [$F(2,51) = 2.96$, $p = 0.07$], that of Block was significant [$F(3,50) = 20.42$, $p = 0.01$], and the interaction Stimulation by Block was not significant [$F(6,47) = 2.07$, $p = 0.06$] (see Table 2). By looking at Table 2 one could realise that the reaction times associated to each type of stimulation (frontal, parietal, or placebo) were rather different – and a p-value of 0.07 support this impression. In particular, the reaction time ‘improvement’ between the first and the fourth block was much larger for the participants receiving verum stimulation (about 1000 ms) than for the participants receiving sham stimulation (about 300 ms). Thus, we calculated the improvement between the first and the fourth block for each group and ran a one-way ANOVA with Stimulation (frontal, parietal, or sham) as independent variable. We found a significant effect of the Stimulation [$F(2,51) = 5.71$, $p = 0.01$], and the Bonferroni post hoc comparison showed that both frontal and parietal stimulation produced a greater improvement than sham stimulation [both $p < 0.05$], while frontal and parietal stimulation did not differ [$p > 0.05$]. Overall, the results of the first experimental session suggested that brain stimulation did not affect participants’ accuracy; additionally, there was evidence that brain stimulation had a limited effect on participants’ reaction times (i.e. when the first and the fourth block were compared), thus suggesting that tRNS had a ‘mild’ immediate benefit on the arithmetic task.

Table 1
Percentage accuracy (averages and standard deviations) in the subtraction verification task across the four consecutive experimental blocks performed in the first session, where three types of brain stimulation were used. The chance level is 50%.

Stimulation	1st block	2nd block	3rd block	4th block
Frontal	79.4	84.0	86.6	84.4
	(17.5)	(10.5)	(7.9)	(13.0)
Parietal	76.6	89.0	88.6	90.3
	(19.8)	(6.4)	(10.4)	(6.7)
Sham	76.0	78.5	83.2	78.8
	(17.0)	(13.3)	(9.9)	(15.5)

Table 2
Reaction times in ms (averages and standard deviations) in the subtraction verification task across the four consecutive experimental blocks performed in the first session, where three types of brain stimulation were used.

Stimulation	1st block	2nd block	3rd block	4th block
Frontal	4107.6	3417.6	3103.5	3033.9
	(1422.4)	(1136.9)	(1279.3)	(1547.4)
Parietal	4154.5	3699.5	3157.1	2761.3
	(1354.7)	(1321.7)	(1256.2)	(1143.5)
Sham	4412.0	4209.7	3914.9	4093.3
	(1142.4)	(1652.2)	(1400.3)	(1102.4)

Thirdly, we ran a two-way ANOVA on the percentage of correct responses in the second session (the one ran 7 days later) with Stimulation (frontal, parietal, or sham) and Novelty (old or new subtractions) as independent variables. The effect of Stimulation was significant [$F(2,51) = 3.47$, $p = 0.04$], suggesting that the brain stimulation received seven days before affected performance in the arithmetic task. The Bonferroni post hoc comparison revealed that both frontal and parietal stimulation improved the arithmetic performance as compared to the sham [both $p < 0.05$] and that there was no difference between frontal and parietal stimulation [$p > 0.05$]. The effect of Novelty was not significant [$F(1,52) = 1.84$, $p = 0.18$] and indicated that old and new subtractions were performed at equivalent accuracy levels. The interaction Stimulation by Novelty was not significant [$F(4,49) = 0.85$, $p = 0.44$] (see Fig. 1).

The same analysis (two-way ANOVA) was repeated for reaction times for correct trials. Here no comparison was significant: Stimulation [$F(2,51) = 0.32$, $p = 0.72$], Novelty [$F(1,52) = 2.08$, $p = 0.15$], and the interaction Stimulation by Novelty [$F(4,49) = 0.01$, $p = 0.99$] (see Table 3).

In the first experimental session, participants were tested on one set of subtractions while in the second session participants were tested on two sets of intermixed subtractions (old and new ones). We opted for intermixed old and new subtractions rather than one block of old and one block of new subtractions to do not over-complicate the design (i.e. do not have to counterbalance the occurrence of the blocks); additionally, to detect skills generalisation, intermixed subtractions made ‘less obvious’ which subtractions were old and which were new. Therefore, a direct comparison between performances in the first and the second experimental sessions would not provide useful information.

Fourthly, to investigate the specificity of tRNS we examined the performance in the distracting task (word categorisation). We calculated the average accuracy and ran a two-way ANOVA with Stimulation (frontal, parietal, or sham) and Time (first or second session) as independent variables. The effect of Stimulation was not significant [$F(2,39) = 1.51$, $p = 0.23$], suggesting that tRNS did

[2] On the computer screen appeared adjectives (e.g. friendly, hostile, honest, indecent, etc.) that were categorised as ‘good’ or ‘bad’ by pressing buttons.

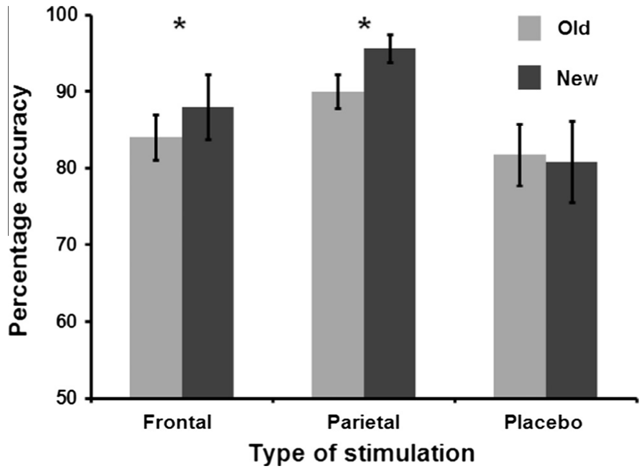

Fig. 1. Percentage accuracy in the subtraction verification task during the second session. Three types of brain stimulation and two sets of stimuli (old and new) were used. Chance level is 50%. Error bars represent the ±SEM.

Table 3
Reaction times in ms (averages and standard deviations) in the subtraction verification task performed in the second session. Three types of brain stimulation and two types of stimuli (old and new) were employed.

Stimulation	Old	New
Frontal	2994.6 (1318.0)	2875.1 (1282.7)
Parietal	3101.7 (1349.6)	2991.7 (1215.9)
Sham	3318.7 (1239.5)	3204.5 (1216.3)

not affect word categorisation; frontally stimulated participants had an accuracy of 94.8% (SD = 4), parietally stimulated participants of 92.8% (SD = 4.1), and placebo participants had an accuracy of 95% (SD = 3.9). The variable Time was not significant [$F(2,39) = 0.33$, $p = 0.57$]; in the first session accuracy was 94.3% (SD = 3.7) and in the second session it was 94.1% (SD = 4.3). The interaction Stimulation by Time was not significant [$F(4,37) = 1.07$, $p = 0.35$].

4. Discussion

Using electricity to stimulate the brain is a 'classic' idea in science (Priori, 2003; Zago, Ferrucci, Fregni, & Priori, 2008) that underwent a revival recently (Brignani, Ruzzoli, Mauri, & Miniussi, 2013; Fertonani et al., 2011; Nitsche & Paulus, 2000; Penolazzi, Pastore, & Mondini, 2013; Tecchio et al., 2010), and tRNS represents one of the last developments among neuro-stimulation techniques (Cappelletti et al., 2013; Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010; Snowball et al., 2013; Terney et al., 2008).

By testing three groups of participants with equivalent arithmetic skills, we found that stimulation of the dorsolateral prefrontal and the posterior parietal cortices (but not placebo stimulation) produced a limited immediate benefit for reaction times and an improvement in accuracy in the long-term arithmetic skills. Our results also indicated that this advantage generalised to unfamiliar trials (new subtractions).

Traditionally, stimulation of DLPFC has been found to affect performance in working memory tasks (Dockery, Liebetanz, Birbaumer, Malinowska, & Wesierska, 2011; Mulquiney et al., 2011), attentional processes (Gladwin, den Uyl, Fregni, & Wiers, 2012), risk assessment (Fecteau et al., 2007), and mood modulation (Boggio et al., 2008). However, a relatively recent study using tRNS (Snowball et al., 2013) showed that DLPFC is *also* involved in numeric processing, and our results confirmed this finding. Whilst Snowball et al. (2013) merely took into account the DLPFC, we compared the effect of tRNS across DLPFC and PPC. Unlike DLPFC, there is abundant evidence that the posterior parietal cortex is involved in numerical processing (Cappelletti et al., 2013; Cohen Kadosh & Walsh, 2009; Cohen Kadosh et al., 2010; Iuculano & Cohen Kadosh, 2014; Sandrini, Miozzo, Cotelli, & Cappa, 2003). In sum, aside confirming the causal involvement of PPC in arithmetic competence, we found a comparable role of DLPFC confirming more recent evidence (Arsalidou & Taylor, 2011; Snowball et al., 2013; Zamarian et al., 2009). Thus, the question we posed in the Introduction can be asked with: "Both areas modulate arithmetic competence". Seen the amount of evidence suggesting that frontal *and* parietal cortices are involved in arithmetic computation, it is not surprising that our results showed that frontal *and* parietal cortices are involved in arithmetic computation.

The key to explain our results is that both brain areas have been shown to support working memory function (Bor & Owen, 2007; Mulquiney et al., 2011; Ohn et al., 2008; Wu et al., 2014), consisting of short-term storage and online manipulation of information (Baddeley & Hitch, 1974; Imbo et al., 2007). Crucially, both storage and manipulation of information are required to solve the subtractions used in our study. We also found that the effect of tRNS was *specific* for the arithmetic task, because stimulation did not affect the performance of a distracting task that did *not* involve working memory (word categorisation). Another hypothesis to explain our results is that tRNS improved attentional processes, which are also supported by DLPFC (Johnson, Strafella, & Zatorre, 2007; Kane & Engle, 2002) and PPC (Bisley & Goldberg, 2010; Buschman & Miller, 2007). Although this explanation cannot be fully rejected, taking into consideration that the task is relatively simple, short, and that visual stimuli (subtractions) are unambiguously displayed (e.g. no visual search), we believe that in this task the role played by attention is relatively moderate compared to the role of working memory.

New subtractions were performed as accurately as old (familiar) ones, thus suggesting that tRNS improved arithmetic performance. In other words, tRNS facilitated arithmetic proficiency rather than merely improving memory of previously presented material. In addition to the theoretical relevance, our finding has extremely important implications for the treatment of impairments affecting numeric skills, such as dyscalculia and acalculia (Krause & Cohen Kadosh, 2013; Von Aster & Shalev, 2007; Willmes, 2008). In fact, considering our results, neuro-restorative interventions should not be focused on PPC cortex alone, but DLPFC could also be considered as a target area, as our findings substantiated its role in numeric competence. This cortical area is strongly connected with working memory function (Dockery et al., 2011; Mulquiney et al., 2011), which is necessary for arithmetic competence (for literature on acalculia and working memory see McLean & Hitch, 1999; Rotzer et al., 2009; Wilson & Swanson, 2001). Thus, this finding could potentially provide an avenue for neuro-restorative interventions in cases of focal parietal damage due to accident, ischaemia, surgery, etc. It should be noted that tRNS improved performance in a *basic* arithmetic operation (subtraction), which is exploited on daily basis and thus of greater practical relevance than more complex arithmetic computations (Beddington et al., 2008).

The benefit of tRNS on a basic calculation ability observed in our study was both immediate (weak and limited to reaction times) and delayed (limited to accuracy scores). A possible explanation for these partial effects is the short exposure to tRNS (one 20-min session). In fact, most studies investigating the effect of brain stimulation (e.g. Cohen Kadosh et al., 2010) for a longer amount of time and for multiple sessions. We opted for a less strenuous protocol and, nevertheless, we were able to find significant immediate *and* delayed effects and generalisation of the benefit to new trials. Follow-up studies might investigate the use of more intense training.

The delayed behavioural effect produced by tRNS has been extensively reported by numerous studies (Cappelletti et al., 2013; Cohen Kadosh et al., 2010; Dockery et al., 2009; Jones, Gözenman, & Berryhill, 2014; Nitsche et al., 2006; Pasqualotto, Kobanbay, & Proulx, 2015; Snowball et al., 2013). In particular, Cohen Kadosh et al. (2010) and Snowball et al. (2013) reported that brain stimulation produced a benefit on numeric competence that lasted at least six months.

A rather speculative explanation of this result is that electric stimulation might facilitate the neural reactivation occurring during sleep (Kuo & Nitsche, 2012; Marshall, Mölle, Hallschmid, & Born, 2004). In fact, during sleep occurs the reactivation of the neurons that used to be active during wakefulness (Abel, Havekes, Saletin, & Walker, 2013; Huber, Ghilardi, Massimini, & Tononi, 2004; Nadel & Moscovitch, 1997) and this process leads to long-term memory consolidation (McGaugh, 2000; Rioult-Pedotti, Friedman, & Donoghue, 2000). Since brain stimulation (and tRNS in particular, Fertonani et al., 2011; Terney et al., 2008) increases neural activity then the stimulated neurons would be more likely to reactivate during sleep. Thus, in our case, the working memory strategies used during the arithmetic task would be better remembered by the participants who received verum brain stimulation. Indeed, further studies (e.g. involving sleep deprivation) are necessary to test this hypothesis in greater detail.

Nevertheless, we showed that tRNS could successfully improve arithmetic skills. We found a causal link between this skill and the parietal cortex (confirmation of 'traditional' results) and the frontal cortex (confirmation recent results) (see also Arsalidou & Taylor, 2011; Zamarian et al., 2009). The frontal cortex might be involved in subtraction borrowing, as reported by Imbo et al. (2007). Additionally, we found that old and new subtractions were performed equally well, thus tRNS seems to improve arithmetic skills rather than merely facilitating memory for previously presented material (Mulquiney et al., 2011). Due to the importance of basic arithmetic calculations in our daily lives, our results bear substantial socio-economic relevance (Beddington et al., 2008).

Acknowledgements

This work was supported by a Marie Curie Intra-European Fellowship (grant number: PIEF-GA-2010-274163). We thank R Cohen Kadosh and his lab for fruitful discussions and advice, and M Uesaki for commenting an earlier version of this manuscript.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nlm.2016.05.004.

References

Abel, T., Havekes, R., Saletin, J. M., & Walker, M. P. (2013). Sleep, plasticity and memory from molecules to whole-brain networks. *Current Biology, 23*, 774–788.
Ambrus, G. G., Paulus, W., & Antal, A. (2010). Cutaneous perception thresholds of electrical stimulation methods: Comparison of tDCS and tRNS. *Clinical Neurophysiology, 121*, 1908–1914.
Anderson, S., Damasio, A., & Damasio, H. (1990). Troubled letters but not numbers: Domain specific cognitive impairments following focal damage in frontal cortex. *Brain, 113*, 749–766.
Arsalidou, M., & Taylor, M. J. (2011). Is 2 + 2 = 4? Meta-analyses of brain areas needed for numbers and calculations. *NeuroImage, 54*, 2382–2393.
Baddeley, A. D., & Hitch, G. J. (1974). Working memory. In G. A. Bower (Ed.), *The psychology of learning and motivation* (pp. 47–89). New York: Academic Press.
Baddeley, A. D. (2000). Short-term and working memory. In E. Tulving & F. I. M. Craik (Eds.), *The Oxford handbook of memory* (pp. 77–92). New York: Oxford University Press.
Beddington, J., Cooper, C. L., Field, J., Goswami, U., Huppert, F. A., Jenkins, R., et al. (2008). The mental wealth of nations. *Nature, 455*, 1057–1060.
Bisley, J. W., & Goldberg, M. E. (2010). Attention, intention, and priority in the parietal lobe. *Annual Review of Neuroscience, 33*, 1–21.
Boggio, P. S., Rigonatti, S. P., Ribeiro, R. B., Myczkowski, M. L., Nitsche, M. A., Pascual-Leone, A., et al. (2008). A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology, 11*, 249–254.
Bor, D., & Owen, A. M. (2007). A common prefrontal–parietal network for mnemonic and mathematical recoding strategies within working memory. *Cerebral Cortex, 17*, 778–786.
Brignani, D., Ruzzoli, M., Mauri, P., & Miniussi, C. (2013). Is transcranial alternating current stimulation effective in modulating brain oscillations. *PLoS ONE, 8*, e56589.
Bueti, D., & Walsh, V. (2009). The parietal cortex and the representation of time, space, number and other magnitudes. *Philosophical Transactions of the Royal Society B: Biological Sciences, 364*, 1831–1840.
Buschman, T. J., & Miller, E. K. (2007). Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science, 315*, 1860–1862.
Butterworth, B., Varma, S., & Laurillard, D. (2011). Dyscalculia: From brain to education. *Science, 332*, 1049–1053.
Capone, F., Capone, G., Ranieri, F., Di Pino, G., Oricchio, G., & Di Lazzaro, V. (2014). The effect of practice on random number generation task: A transcranial direct current stimulation study. *Neurobiology of Learning and Memory, 114*, 51–57.
Cappelletti, M., Gessaroli, E., Hithersay, R., Mitolo, M., Didino, D., Kanai, R., et al. (2013). Transfer of cognitive training across magnitude dimensions achieved with concurrent brain stimulation of the parietal lobe. *Journal of Neuroscience, 33*, 14899–14907.
Cohen Kadosh, R., Soskic, S., Iuculano, T., Kanai, R., & Walsh, V. (2010). Modulating neuronal activity produces specific and long-lasting changes in numerical competence. *Current Biology, 20*, 2016–2020.
Cohen Kadosh, R., & Walsh, V. (2009). Numerical representation in the parietal lobes: Abstract or not abstract? *Behavioral and Brain Sciences, 32*, 313–328.
Dockery, C. A., Hueckel-Weng, R., Birbaumer, N., & Plewnia, C. (2009). Enhancement of planning ability by transcranial direct current stimulation. *Journal of Neuroscience, 29*, 7271–7277.
Dockery, C. A., Liebetanz, D., Birbaumer, N., Malinowska, M., & Wesierska, M. J. (2011). Cumulative benefits of frontal transcranial direct current stimulation on visuospatial working memory training and skill learning in rats. *Neurobiology of Learning and Memory, 96*, 452–460.
Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., & Pascual-Leone, A. (2007). Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: A direct current stimulation study. *Journal of Neuroscience, 27*, 12500–12505.
Fertonani, A., Ferrari, C., & Miniussi, C. (2015). What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects. *Clinical Neurophysiology, 126*, 2181–2188.
Fertonani, A., Pirulli, C., & Miniussi, C. (2011). Random noise stimulation improves neuroplasticity in perceptual learning. *The Journal of Neuroscience, 31*, 15416–15423.
Fertonani, A., Rosini, S., Cotelli, M., Rossini, P. M., & Miniussi, C. (2010). Naming facilitation induced by transcranial direct current stimulation. *Behavioural Brain Research, 208*, 311–318.
Galfano, G., Penolazzi, B., Vervaeck, I., Angrilli, A., & Umiltà, C. (2009). Event-related brain potentials uncover activation dynamics in the lexicon of multiplication facts. *Cortex, 45*, 1167–1177.
Gladwin, T. E., den Uyl, T. E., Fregni, F. F., & Wiers, R. W. (2012). Enhancement of selective attention by tDCS: Interaction with interference in a Sternberg task. *Neuroscience Letters, 512*, 33–37.
Hecht, S. A. (2002). Counting on working memory in simple arithmetic when counting is used for problem solving. *Memory and Cognition, 30*, 447–455.
Hitch, G. J. (1978). The role of short-term working memory in mental arithmetic. *Cognitive Psychology, 10*, 302–323.
Homan, R. W., Herman, J., & Purdy, P. (1987). Cerebral location of international 10–20 system electrode placement. *Electroencephalography and Clinical Neurophysiology, 66*, 376–382.
Huber, R., Ghilardi, M. F., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature, 430*, 78–81.
Imbo, I., Vandierendonck, A., & Vergauwe, E. (2007). The role of working memory in carrying and borrowing. *Psychological Research, 71*, 467–483.
Iuculano, T., & Cohen Kadosh, R. (2014). Preliminary evidence for performance enhancement following parietal lobe stimulation in developmental dyscalculia. *Frontiers in Human Neuroscience, 8*, 38.
Johnson, J. A., Strafella, A. P., & Zatorre, R. J. (2007). The role of the dorsolateral prefrontal cortex in bimodal divided attention: Two transcranial magnetic stimulation studies. *Journal of Cognitive Neuroscience, 19*, 907–920.
Jones, K. T., Gözenman, F., & Berryhill, M. E. (2014). Enhanced long-term memory encoding after parietal neurostimulation. *Experimental Brain Research, 232*, 4043–4054.
Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychonomic Bulletin & Review, 9*, 637–671.

Krause, B., & Cohen Kadosh, R. (2013). Can transcranial electrical stimulation improve learning difficulties in atypical brain development? A future possibility for cognitive training. *Developmental Cognitive Neuroscience, 6*, 176–194.
Kuo, M. F., & Nitsche, M. A. (2012). Effects of transcranial electrical stimulation on cognition. *Clinical EEG and Neuroscience, 43*, 192–199.
Logie, R. H., Gilhooly, K. J., & Wynn, V. (1994). Counting on working memory in arithmetic problem solving. *Memory and Cognition, 22*, 395–410.
Marshall, L., Mölle, M., Hallschmid, M., & Born, J. (2004). Transcranial direct current stimulation during sleep improves declarative memory. *Journal of Neuroscience, 24*, 9985–9992.
McGaugh, J. L. (2000). Memory – A century of consolidation. *Science, 287*, 248–251.
McLean, J. F., & Hitch, G. J. (1999). Working memory impairments in children with specific arithmetic learning difficulties. *Journal of Experimental Child Psychology, 74*, 240–260.
Mulquiney, P. G., Hoy, K. E., Daskalakis, Z. J., & Fitzgerald, P. B. (2011). Improving working memory: Exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. *Clinical Neurophysiology, 122*, 2384–2389.
Mussolin, C., Mejias, S., & Noël, M. P. (2010). Symbolic and nonsymbolic number comparison in children with and without dyscalculia. *Cognition, 115*, 10–25.
Nadel, L., & Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Current Opinions in Neurobiology, 7*, 217–227.
Nitsche, M. A., Lampe, C., Antal, A., Liebetanz, D., Lang, N., Tergau, F., et al. (2006). Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. *European Journal of Neuroscience, 23*, 1651–1657.
Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology, 527*, 633–639.
Ohn, S. H., Park, C. I., Yoo, W. K., Ko, M. H., Choi, K. P., Kim, G. M., et al. (2008). Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. *NeuroReport, 19*, 43–47.
Pasqualotto, A., Kobanbay, B., & Proulx, M. J. (2015). Neural stimulation has a long-term effect on foreign vocabulary acquisition. *Neural Plasticity, 2015* Article ID 671705.
Paulus, W. (2011). Transcranial electrical stimulation (tES–tDCS; tRNS, tACS) methods. *Neuropsychological Rehabilitation, 21*, 602–617.
Penolazzi, B., Pastore, M., & Mondini, S. (2013). Electrode montage dependent effects of transcranial direct current stimulation on semantic fluency. *Behavioural Brain Research, 248*, 129–135.
Penolazzi, B., Stramaccia, D. F., Braga, M., Mondini, S., & Galfano, G. (2014). Human memory retrieval and inhibitory control in the brain: Beyond correlational evidence. *Journal of Neuroscience, 34*, 6606–6610.
Priori, A. (2003). Brain polarization in humans: A reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clinical Neurophysiology, 114*, 589–595.
Rioult-Pedotti, M. S., Friedman, D., & Donoghue, J. P. (2000). Learning-induced LTP in neocortex. *Science, 290*, 533–536.
Rotzer, S., Loenneker, T., Kucian, K., Martin, E., Klaver, P., & Von Aster, M. (2009). Dysfunctional neural network of spatial working memory contributes to developmental dyscalculia. *Neuropsychologia, 47*, 2859–2865.
Sandrini, M., Miozzo, A., Cotelli, M., & Cappa, S. F. (2003). The residual calculation abilities of a patient with severe aphasia: Evidence for a selective deficit of subtraction procedures. *Cortex, 39*, 85–96.
Snowball, A., Tachtsidis, I., Popescu, T., Thompson, J., Delazer, M., Zamarian, L., et al. (2013). Long-term enhancement of brain function and cognition using cognitive training and brain stimulation. *Current Biology, 23*, 987–992.
Tecchio, F., Zappasodi, F., Assenza, G., Tombini, M., Vollaro, S., Barbati, G., et al. (2010). Anodal transcranial direct current stimulation enhances procedural consolidation. *Journal of Neurophysiology, 104*, 1134–1140.
Terney, D., Chaieb, L., Moliadze, V., Antal, A., & Paulus, W. (2008). Increasing human brain excitability by transcranial high-frequency random noise stimulation. *Journal of Neuroscience, 28*, 14147–14155.
Von Aster, M. G., & Shalev, R. S. (2007). Number development and developmental dyscalculia. *Developmental Medicine and Child Neurology, 49*, 868–873.
Willmes, K. (2008). Acalculia. In G. Goldenberg & B. L. Miller (Eds.), *Handbook of clinical neurology* (pp. 339–358). Amsterdam: Elsevier.
Wilson, K. M., & Swanson, H. L. (2001). Are mathematics disabilities due to a domain-general or a domain-specific working memory deficit? *Journal of Learning Disabilities, 34*, 237–248.
Wu, Y. J., Tseng, P., Chang, C. F., Pai, M. C., Hsu, K. S., Lin, C. C., et al. (2014). Modulating the interference effect on spatial working memory by applying transcranial direct current stimulation over the right dorsolateral prefrontal cortex. *Brain and Cognition, 91*, 87–94.
Zago, S., Ferrucci, R., Fregni, F., & Priori, A. (2008). Bartholow, Sciamanna, Alberti: Pioneers in the electrical stimulation of the exposed human cerebral cortex. *The Neuroscientist, 14*, 521–528.
Zamarian, L., Ischebeck, A., & Delazer, M. (2009). Neuroscience of learning arithmetic—Evidence from brain imaging studies. *Neuroscience and Biobehavioral Reviews, 33*, 909–925.