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Short and long-term effects of sham-controlled prefrontal EEG-neurofeedback training in healthy subjects

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HIGHLIGHTS

- Controlled EEG neurofeedback study in adult healthy subjects using a novel sham design.
- Altered frontal beta activity in healthy subjects after 15 EEG neurofeedback training sessions.
- Demonstration of long-term effects using resting state EEG after three years.

ABSTRACT

Objective: In this study we evaluated long-term effects of frontal beta EEG-neurofeedback training (E-NFT) on healthy subjects. We hypothesized that E-NFT can change frontal beta activity in the long-term and that changes in frontal beta EEG activity are accompanied by altered cognitive performance.
Methods: 25 healthy subjects were included and randomly assigned to active or sham E-NFT. On average the subjects underwent 15 E-NFT training sessions with a training duration of 45 min. Resting-state EEG was recorded prior to E-NFT training (*t*1) and in a 3-year follow-up (*t*3).
Results: Compared to sham E-NFT, which was used for the control group, real E-NFT increased beta activity in a predictable way. This increase was maintained over a period of three years post training. However, E-NFT did not result in significantly improved cognitive performance.
Conclusion: Based on our results, we conclude that EEG-NFT can selectively modify EEG beta activity both in short and long-term.
Significance: This is a sham controlled EEG neurofeedback study demonstrating long-term effects in resting state EEG.

1. Introduction

Neurofeedback training (NFT) is a neurophysiological training method for altering brain activity. It is thought to be based on the principle of operant conditioning. Operant conditioning is a key ability of neural systems to link the contingency of the reward signal to the probability of a future reward (Arns et al., 2009; Larsen and Sherlin, 2013; Gruzelier, 2014a). EEG is recorded and is fed back in real-time by means of auditory and/or visual feedback. Reinforcement is provided when a desired pattern of brain activity/EEG is held for a certain amount of time. However, the specific underlying mechanisms of NFT efficacy are still unclear and are under systematic investigation (Gruzelier, 2014a,b). Research on EEG-NFT (E-NFT) in healthy subjects has been completed in both animal and human studies. Monkeys are able to voluntarily control neuronal activity by means of simple auditory or visual feedback resulting in strong oscillatory activity changes within five training sessions (Philippens and Vanwersch, 2010). In humans, previous studies found an enhancement of beta activity in the frontal brain after neurofeedback training (Zoefel et al., 2011; Zotev et al., 2014). Cognitive enhancement regarding neurofeedback training in healthy subjects has been efficaciously established in the past (Gruzelier, 2014a,b). There is data demonstrating the change of neuronal activity measured with EEG after EEG

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neurofeedback training, but there is also a direct link to fMRI changes. Ros and colleagues trained healthy subjects to suppress the alpha frequency band (8–12 Hz) and found by means of fMRI that the default mode network connectivity was altered and inversely correlated with EEG alpha changes for a prolonged time period of 30 min (Ros et al., 2013).

As also mentioned in the recent study of Arns and Kenemans (2014), there are indications that E-NFT can induce long-term effects in patients with attention deficit/hyperactivity disorder (ADHD) (Strehl et al., 2006; Leins et al., 2007) and in healthy subjects (Gevensleben et al., 2014). However, so far it has not been investigated in a randomized sham controlled study, whether E-NFT will remain stable over multiple years in healthy subjects.

Our hypotheses were as follows: (1) there will be cognitive changes after frontal beta E-NFT; (2) an increase of resting state EEG beta power (12–18 Hz) at Fz is expected directly after a series of E-NFT; (3) an increase of resting state EEG beta power (12–18 Hz) at Fz is expected after a period of three years post training.

2. Subjects and methods

The study was approved by the Scientific and Ethical Review Committee at the Faculty of Psychology and Education (VCWE) at the VU University of Amsterdam. Subjects were recruited via email or by phone and agreed to participate by written informed consent. They were informed that they could either be part of the experimental or the control group.

2.1. Subjects

25 healthy subjects (19 women, 6 men) participated in this study. All of them were first-year psychology students of the Free University (VU) in Amsterdam and were compensated with elective credit points for participation. The students were randomly assigned to either sham or control group by use of the random sample function of SPSS with a sample size of approximately 50% of all cases for both groups. This procedure was separately applied to both male and female students. A Mann–Whitney test indicated equality of the age within the groups. (Average of 241.1 months for group 1 and 253.2 months for group 2; $U = 43.5$, $N1 = 11$, $N2 = 14$, $p < 0.63$, two-tailed.) There were no sociodemographic differences between the groups at the three time points of measurement. Three participants, one male subject of the experimental group and two women of the control group, dropped out before the start of the study due to personal reasons. Thus, the real E-NFT group consisted of ten subjects (three men, average age 19.7 years, SD 2.6, range 18–25 years), the sham group consisted of 12 subjects (two men, average age 21.08 years, SD 3.85, range 18–32 years), who underwent the study procedures as described below. Three participants (2 control) did not show up during the post EEG measurement procedure. After a period of three years, all subjects were contacted via email or by phone and asked to voluntarily participate in the follow-up study. After three years, ten participants (45, 5%) completed the follow-up measurements. At long-term follow-up, the real E-NFT group consisted of two men and three women ($n = 5$, mean age 23.33 years, SD 3.26, range 20.99–28.14 years) and the control sham group of five women ($n = 5$, mean age 23.59 years, SD 2.15, range 20.99–26.25 years). See Fig. 1 for schematic representation of the study design.

2.2. Methods

EEGs were recorded using a Deymed Truscan 32-channel EEG amplifier in combination with a 19-channel electrode cap. Electrode skin impedance was kept below 5 kΩ. The sampling rate was 128 Hz. Electrodes were placed according to the International 10/20 System (Jaspers, 1958). An electrode at Fpz served as ground electrode. The EEG system was connected to a portable computer. EEG was analyzed by means of the program Insight II (Version 2004.11.22, Persyst Development Corporation, Prescott, Arizona) for qualitative analysis. For quantitative analysis NeuroGuide (Version 2.7.5) was used. A 4-channel Deymed BFB III system was used for the neurofeedback trainings. The system was connected to a laptop computer via BFB III software, output was given to two separate headphones and two separate 15″ RCT monitors with 2 ms delay in transfer time.

2.3. Study procedures

Cognitive performance was measured by use of an abbreviated version of the Groninger Intelligentie Test (GIT) (Luteijn and Barelds, 2004) at measurement 1 and 2, combined with a digital version of 9 mazes, which are part of the digital test program Digoloog (Engelbregt et al., 2004). Since we found no time *x* group effect between measurements 1 and 2 (Engelbregt et al., 2010), we decided to skip the digital tests of the protocol to reduce the effort of the participants. Therefore, only the abbreviated GIT pen and paper tests were taken at measurement 1 (*t*1), 2 (*t*2) and 3 (*t*3).

Baseline EEG was captured one week previous to the E-NFT training sessions. The post measurement was performed within one week after the final training session and the follow-up after approximately three years post training, during both eyes open and eyes closed condition. On average, the total duration of EEG measurements was 30 min. The resting state EEG was recorded for 5 min during eyes closed (EC) and for 5 min during eyes open (EO). Subjects were sitting in a comfortable seat and were

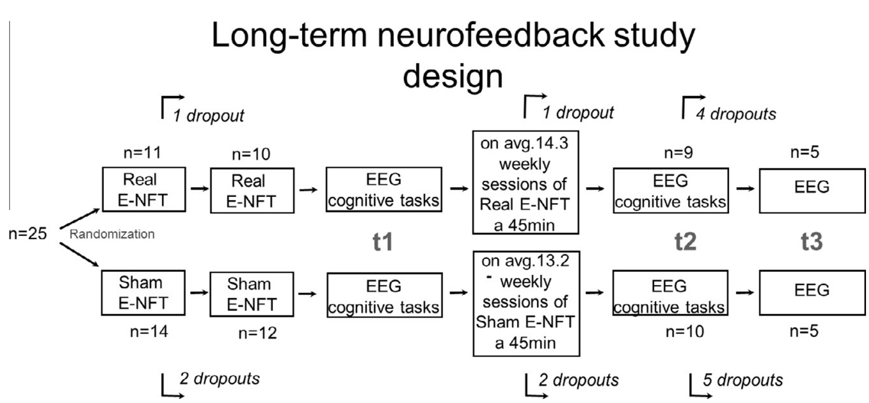

Fig. 1. Illustration of the study design.

instructed to relax and to avoid eye blinks. The lab was located in a sound attenuated room. All EEG recordings were done in a time-frame of between 9 am and 1 pm, before lunch break. Although we aimed to do an average of 15 training sessions, an average of respectively 14.3 (within a range of 13–15 trainings) and 13.2 (within a range of 13–15 trainings) trainings were completed for the experimental and the sham group. Trainings were aimed to enhance 12–18 Hz beta activity within the range of one central frontally located electrode (Fz according to the International 10–20 System for electrode placement (Jaspers, 1958). In order to control possible benefits of facial muscle contractions, an increase of 35–45 Hz activity overruled the possible reward due to increasing 12–18 Hz activity. There was no averaging of EEG data, which practically meant that subjects received real-time EEG feedback as long as the state continued for a minimum of 1 s. Each training session took approximately 45 min, of which two minutes were used for measuring baseline signals of EC and EO conditions respectively. Trainings consisted of 10 different three minute games. The study instructor rewarded parameters on an ad-hoc basis leading to an average score of about 15 points per game session. Both discrete and continuous auditory and visual feedback of EEG parameters were offered to the subjects. One example of continuous visual feedback is a videogame where a swimming dolphin appears as soon as the activity of both 12–18 Hz is increased and 35–45 Hz is inhibited. If this situation endures for longer than one second, a score of one is being earned, which is accompanied by an auditory, rewarding sound. The latter is known as discrete feedback. Subjects in the control sham group were given exactly the same feedback as the neighbor subject of the real E-NFT group. Since there was no connection between their brain activity and feedback, we expect no unconscious learning effect considering the increase of 12–18 Hz frontal lobe activity. A folding screen was placed between subjects of both groups, so no one could see what was displayed on the other screen. See Figs. 1 and 2 for details of the study procedures and the setting.

The study instructor was unaware of the condition since a second instructor put electrodes in the EEG amplifier that was placed on top of the separating wall between the subjects (black line). The electrodes of the sham subject were placed in an inactive channel slot of the recorder. A blanket was placed on top of the EEG recorder to prevent the trainer from gaining any information of the subject's condition. Curious subjects who asked for more information about the sham condition were held back regarding any technical details and referred to the end of the study. After the final training

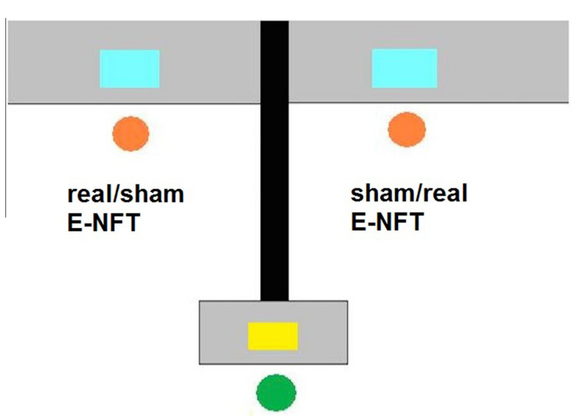

Fig. 2. Presentation of the study settings: the green dot represents the instructor of the study, the orange dots represent both subjects that were randomly assigned to the real E-NFT or to the sham E-NFT condition. The subjects were separated by a folding screen. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

session, all participants were asked about their experience of the training. None of them mentioned any doubt about the experimental condition of the training. Only after the follow-up measurement, three years later, interested subjects were informed whether they were in the sham or in the experimental condition.

2.3.1. EEG recordings and selections

22 participants took part in the pre-training measurement procedure, 19 of which were present at the post-measurement after the training procedure and 10 attended the follow-up after three years. One entire individual EEG recording lasted about 10 min. For quantitative analyses Laplacian montage was used for the comparison between conditions.

Data selection for the EEG analysis was done by a neuropsychologist (H.E.). These data were verified by an independent EEG expert (D.K.).

2.3.2. EEG transformations and analyses

Prior to both analyses, EEG recordings were screened by a neurologist for seizure activity and/or abnormal EEG patterns (J.F.). There were no signs of any abnormality. Data of individual EEG recordings were included only when there was a minimum of 30 s artifact free data. For two subjects, the total amount of artifact free data was too low during the post-training recording ($t2$). This was due to a defect electrode in the EEG cap. For the analysis, the absolute power data of 12–18 Hz of the target electrode Fz and the other frontal areas (FP1, FP2, F3, F4, F7 and F8) were included. Data sets were analyzed with SPSS Version 22. Data of both open- and closed eyes conditions of 12–18 Hz were included for the selection of outliers. Outliers (5% trimmed mean) were found by creating z-scores using the descriptives function in SPSS, and by ignoring those scores ($-2.3 \leqslant z \geqslant 2.3$) by labeling them as missing values. Thus outliers were ignored for the described analyses. For eyes open, there were 7 subjects left in both experimental and sham group for the comparison of measurement 1 ($t1$) and measurement 2 ($t2$). For closed eyes the number of subjects was 10 and 7, respectively. For the comparison of $t1$ and the follow up ($t3$) there were 5 couples for the eyes open- and 4 for the eyes closed comparison. For eyes open, there were a maximum of 10 subjects left in the experimental and 7 in the sham group for the comparison of measurement 1 ($t1$) and measurement 2 ($t2$). For closed eyes the number of subjects was 10 and 7, respectively. For the comparison of $t1$ and the follow up ($t3$) there were a maximum of 5 in the experimental and 5 in the sham group for both the eyes open comparison as for eyes closed.

Due to the relatively high variability between the number of subjects of $t1$–$t2$ and $t3$, with only a maximum of 19 retested participants, we transformed the data into z-scores using Shapiro Wilk test in order to demonstrate relevant figures (see Fig. 3). Repeated measures ANOVA were conducted to evaluate whether there was an interaction between group and time with regard to EEG power (μV^2) between the experimental (E-NFT) and the sham group. The between-subject factor was *group* with two levels (experimental and control, respectively) and the within-subject factor was *time* with two levels (baseline and post-training baseline and follow-up, respectively). The effects were analyzed post hoc using paired-samples t tests, in order to gain insight into existing significant interactions. For the other frontal channels we also conducted Bonferroni corrected repeated measures ANOVA, only to gain insight into the specificity of the found effects.

2.3.3. LORETA analysis

A surface recorded scalp EEG with eyes closed was used for a 3D current density analysis using the LORETA package v20150415 (http://www.uzh.ch/keyinst/loreta.htm). LORETA estimates the current source density ($\mu V/mm^2$) distribution of each voxel at

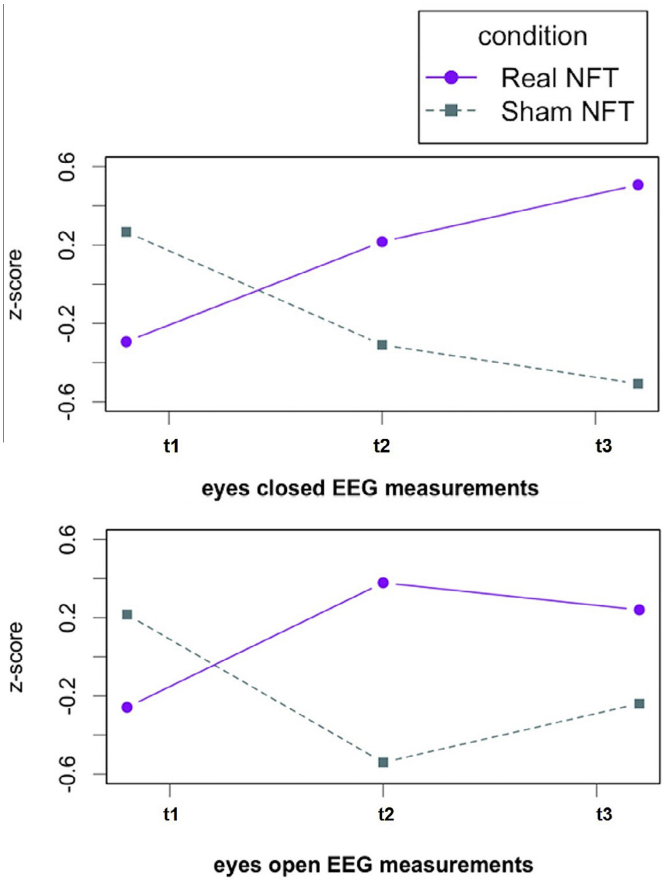

Fig. 3. Interaction effects of group (real E-NFT and sham E-NFT) *x* time for 12–18 Hz frequency band of EEG electrode Fz. Displayed are mean *z*-scored power differences of both eyes closed and eyes open for measurement 1–2 ($t1$–$t2$) and measurement 1–3 ($t1$–$t3$), respectively.

5 mm spatial resolution (low resolution) in the Talairach/MNI space. A detailed description of the sLORETA method is explained by Pascual-Marqui (2002). The scalp EEG was segmented into 2s segments and converted into cross spectrum files for the discrete frequency range of 12–18 Hz using the sLORETA transformation matrix in order to convert the electrical scalp activity into standardized current density in the cortex. Due to the variability of structural brain tissue and conductivity levels in small sample sizes we used a subject-wise data normalization to eliminate a global source of variability. Nine subjects were included for the comparison $t2$ vs. $t1$ resting state EEG data, for the conditions eyes closed and eyes open (18 EEG data sets). For the five remaining subjects, the comparison $t3$ vs. $t1$ resting state EEG data was used again for the condition eyes closed and eyes open (10 EEG data sets). The statistical comparisons between $t3$ vs. $t1$ and between $t2$ vs. $t1$ were done for real E-NFT and sham E-NFT using the implemented statistical nonparametric mapping tool. The statistical level was set at $p < 0.05$ (two-tailed) and $p < 0.01$ (two-tailed).

3. Results

3.1. EEG

The results indicate significant time *x* group interaction effects for channel Fz for closed eyes (EC) conditions between measurement 1 ($t1$) and 2 ($t2$) and measurement 1 and 3 ($t3$). For open eyes (EO), a significant time *x* group interaction effect within subjects was found between $t1$ and $t3$, and a trend towards a significant effect between $t1$ and $t2$ (see Table 1, Fig. 3). No significant effects or trends on other channels were found.

The results of the post hoc paired-samples *t* tests indicate a significant increase of 12–18 Hz activities at $t2$ in comparison to the $t1$ measurement for the experimental group (real E-NFT) in both EC and EO condition on Fz. For eyes open, there was a significant increase of 12–18 Hz activity on location Fz between $t1$ and $t3$ for the experimental group (see Table 2).

3.1.1. sLORETA results

The sLORETA analysis revealed a significant effect in the beta frequency band (12–18 Hz) for the comparison $t2$ vs. $t1$ in frontal brain regions, such as the right and left medial frontal gyrus and the left and right superior frontal gyrus (t_{max} = 6.18, 86 voxels, BA 8, BA 9, BA 6, $p < 0.05$), predominantly in the right hemisphere (Table 3, Fig. 4A). A second larger cluster was found in the right inferior frontal gyrus and the right middle frontal gyrus (t_{max} = 6.05, 36 voxels, BA 45, BA 46, BA 47, $p < 0.05$). Increasing the statistical threshold to $p < 0.01$, a cluster of 9 voxels was found encompassing the right superior frontal gyrus and the right medial frontal gyrus (t_{max} = 6.18, 9 voxels, BA 9, BA 46). For the comparison between $t3$ vs. $t1$, increased beta activity (12–18 Hz) was found in cortical regions, such as the right inferior frontal gyrus and the right superior temporal gyrus (t_{max} = 7.08, 19 voxels, BA 45, BA 47, BA 22, $p < 0.05$), see Table 3, Fig. 4B. We did not find any significant effects for the sham E-NFT group.

3.2. Cognitive tests

There was no indication of altered performances on cognitive tasks due to E-NFT. Only a main effect for time was found, both past the initial series of E-NFT and three years later, $F(2,5) = 7.2$, $p < .05$, $\eta^2 = .74$. There was no significant interaction between group and measurement *t*, $F(2,5) = 0.57$, $p = .6$, $\eta^2 = .19$ (see Fig. 5).

4. Discussion

The key finding of the current study was an increase of 12–18 Hz frontal lobe activity, specifically at Fz location in the experimental group compared to the sham condition within one week after the final E-NFT trainings. Post-hoc *t*-tests showed a significant increase of 12–18 Hz activity in both EC and EO condition between measurement $t1$ and $t2$, and between measurement $t1$ and $t3$ for the EO condition. LORETA source analysis for the resting state, including both conditions EC and EO, showed a significant 12–18 Hz increase in frontal brain regions such as the medial

Table 1
Interaction effects for target channel Fz (mean square, *df*, *F*, and *p*-value) of, group and time of measurement. The table displays the interactions of the differences in EEG power (μV^2, 12–18 Hz frequency band) between measurements $t1$–$t2$ and $t1$–$t3$, respectively, electrode position and group with both eyes closed, eyes open condition. The number of subjects differs due to selection criteria as mentioned in the section 'EEG transformations and analyses'. R = real E-NFT, S = sham E-NFT. *p* values below .05 are marked in bold.

Eyes open /eyes closed	Real E-NFT (*n*)	Sham E-NFT (*n*)	Type of effect	Mean square	*df*	*F*	*p*
EC	10	7	Fz time *x* group $t1$ vs. $t2$	4899	1	5.518	.080
EO	10	7	Fz time *x* group $t1$ vs. $t2$	6085	1	5.722	**.030**
EC	5	4	Fz time *x* group $t1$ vs. $t3$	18973	1	5.757	**.048**
EO	5	5	Fz time *x* group $t1$ vs. $t3$	2375	1	5.485	**.047**

Table 2
Paired sample *t*-tests for EEG power (μV^2) differences on electrode location Fz (12–18 Hz frequency band), measurements *t*1 (baseline) vs. *t*2 (post training), and *t*1 vs. *t*3 (follow-up) for both groups (R, S) and either condition (EC, EO). R: real E-NFT; S: sham E-NFT, EC: eyes closed, EO: eyes open. EEG power differences are presented as mean ± standard deviation (SD) with 95% confidence intervals (CI). *p* values below .05 are marked in bold.

Condition		Mean	SD	95% CI		*t*-value	*df*	*p*
				Lower	Upper			
Fz EC, *t*1–*t*2	R	−53.67	47.85	−87.90	−19.45	−3.55	9	**.006**
Fz EC, *t*1–*t*2	S	−4.89	59.41	−59.84	50.06	−.218	6	.835
Fz EC *t*1–*t*3	R	−90.46	106.01	−222.09	41.17	−1.91	4	.129
Fz EC *t*1–*t*3	S	69.27	67.20	−14.17	152.71	2.305	4	.083
Fz EO *t*1–*t*2	R	−46.02	45.32	−78.44	−13.60	3.21	9	**.011**
Fz EO *t*1–*t*2	S	8.35	47.30	−35.40	52.09	.467	6	.657
Fz EO *t*1–*t*3	R	−170.42	120.97	−320.62	−20.22	−3.15	4	**.035**
Fz EO *t*1–*t*3	S	24.27	19.63	−.11	48.64	2.76	4	.051

Table 3
Statistically significant differences of cortical current density values (LORETA, 12–18 Hz frequency band); clusters of neighboring voxels are depicted in MNI (Montreal Neurological Institute) brain coordinates, Brodman areas, and anatomical regions. First line: comparison *t*3 vs. *t*1, real E-NFT vs. baseline, 3-year-follow-up. Second and third line: *t*2 vs *t*1, real E-NFT vs. baseline after the end of E-NFT-training.

Measurement	Cluster	Voxels (5 * 5 * 5 mm)	*X*, *Y*, *Z* (MNI space), max value	Brodman area	Anatomical region
*t*3–*t*1	1	7	−10, 55, 5	10	Medial frontal gyrus, superior frontal gyrus
*t*2–*t*1	1	9	5, 40, −20	10, 11	Medial frontal gyrus, orbital gyrus, rectal gyrus
*t*2–*t*1	2	8	5, 40, −10	32	Anterior cingulate

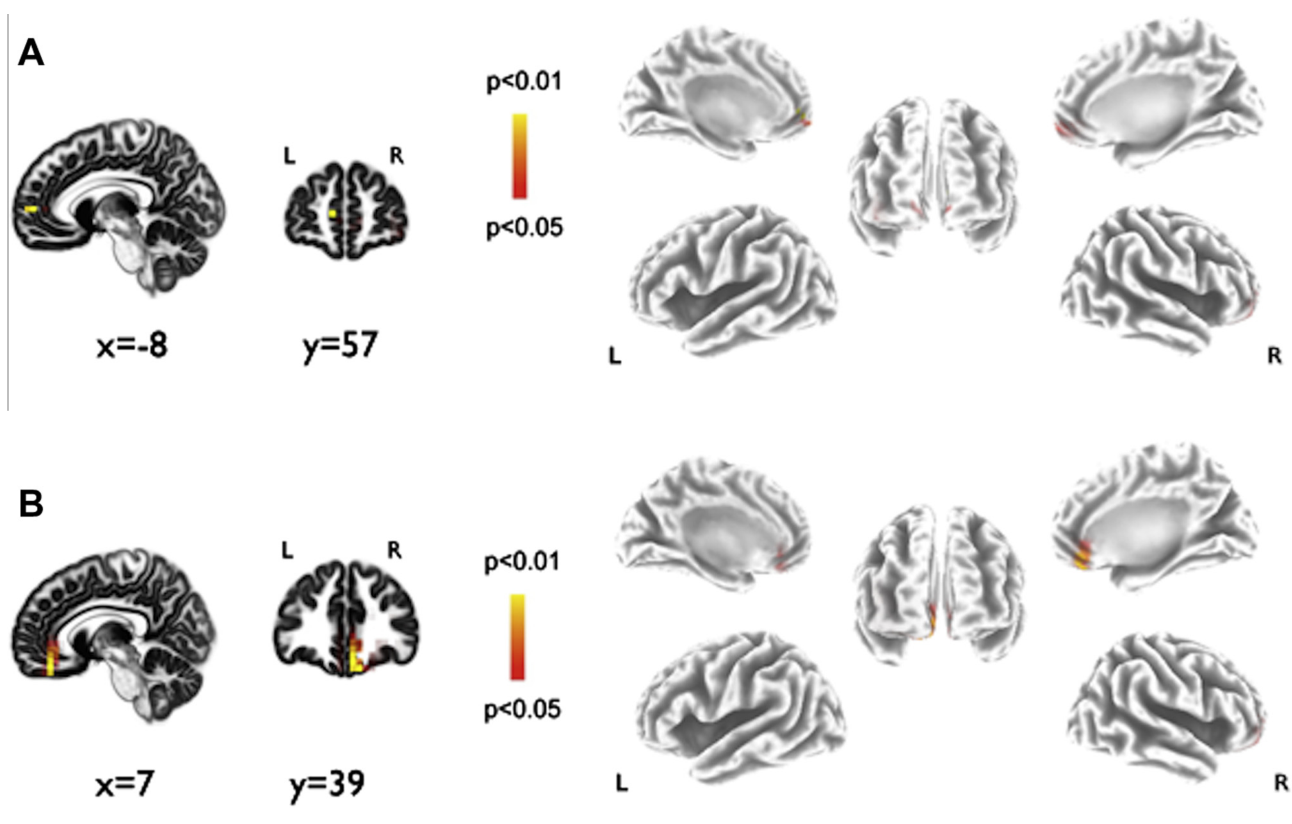

Fig. 4. Long-term effects of E-NFT on a standard volumetric MRI template (left) and on cortical surfaces (right). A. Left: source localization post E-NFT (*t*2 vs. *t*1), increase of 12–18 Hz current density after NFB training at the right and left medial frontal cortex (BA 9) and the left and right superior frontal cortex (BA 8), predominantly in the right hemisphere. Right: cortical surfaces post E-NFT (*t*2 vs. *t*1). B. Left: source localization post E-NFT (*t*3 vs. *t*1), increase of 12–18 Hz current density after NFB training at the right inferior frontal gyrus (BA 45, 47) and the right superior temporal gyrus (BA 22). Right: cortical surfaces post E-NFT (*t*3 vs. *t*1).

frontal cortex and the superior frontal cortex, predominantly in the right hemisphere. The medial distribution of current density is related to the increase in the Fz sensor electrode. It is possible that the low resolution distorted the results slightly. The long-term effects were located even more right sided and also in the superior temporal gyrus. The temporal cortex/hippocampus region is known for long-term potentiation and even though it is speculative, plasticity effects may still occur in the real E-NFT group after three years. The sample size decreased at long-term follow-up, nevertheless, we found that the reported effects in the remaining study participants were stable even three years later at follow-up and remained statistically significant in the open eyes condition.

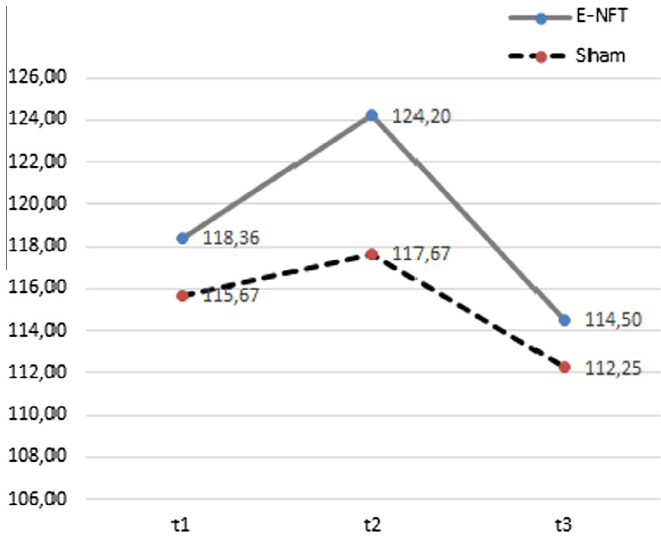

Fig. 5. Averaged IQ scores of both sham E-NFT and real E-NFT group ($t1$ = baseline, $t2$ = week after final training, $t3$ = three years post-training).

As we've only trained with eyes open, the sample size might have been too small to maintain a statistically significant effect for the eyes closed condition. However, the provided data indicate that it might be possible to induce a stable long-term effect after 14 sessions of E-NFT training. The short term-effects are in accordance with early and recent neurofeedback studies using upper EEG alpha or EEG beta frequency training of the frontal brain (Egner and Gruzelier, 2004; Cho et al., 2008; Keizer et al., 2010; Zoefel et al., 2011; Zotev et al., 2014). Based on our results, we conclude that non-invasive EEG-NFT using frontal scalp electrodes can selectively change frontal EEG beta activity, in both short-term and long-term. E-NFT is considered to be based on operant conditioning and in the past it has been shown that healthy subjects can learn to control neuro-electric brain activity by displaying subjects' ongoing changes in the EEG (Elbert et al., 1980; Birbaumer et al., 2000). The process of long-term potentiation (LTP) is suggested to take place by sensitization of neurons after repeated excitation, followed by persistent changing and creation of new synapses and synaptic connections (Kandel, 2006). Using a different non-invasive stimulation approach (continuous theta burst stimulation, cTBS) and a different frontal brain region, McAllister and colleagues found that oscillatory beta activity mediates neuroplastic effects of motor cortex stimulation in humans (McAllister et al., 2013). Regarding our data, we can only speculate whether synaptic strengthening of neurons within frontal brain regions has been induced after continuous reward of beta activity at electrode Fz. Activity in the medial frontal brain region might be more easily induced and is more likely to generate beta 12–18 Hz activity and neuronal-within communication after continuous neurofeedback training sessions. Recently, it was found that 30 min of real-time ACC neurofeedback in healthy subjects induced long-term Hebbian-like restructuring in the following way: Voxels co-activated during the initial training session were found to have increased one day later (Harmelech et al., 2013).

Compared to more passive non-invasive brain stimulation methods (NIBS) such as tDCS or rTMS where effects are lasting for weeks up to months post-treatment, the active involvement of neurofeedback may stabilize training effects. Another main difference between neurofeedback and NIBS is that the latter delivers a fixed stimulation protocol to activate or inactivate certain brain regions, whereas in neurofeedback neuronal activities and responses are individually adjusted and an individualized feedback is applied.

Nevertheless, there are several shortcomings in our study that need to be mentioned. The sample size was low and unfortunately, only 10 of the initial 22 subjects could be included in the longitudinal assessments. Since there were no differences in cognitive performance, the neuropsychological tests used in this study may not have been specific enough to detect subtle changes, because they only globally screened executive capabilities. One alternative explanation would be that the specific neurofeedback protocol in this study was not appropriate to induce cognitive effects in healthy subjects. More specific tasks, such as the n-back or the Go-NoGo-task, should be considered in further study trials. Another explanation for the lack of changes in cognitive function could be a ceiling effect in our sample of healthy, relatively high performing students.

Altogether, our subjects underwent about 302 forty-five minute neurofeedback sessions. The long-term data of study participants remained stable and statistically significant for the EO condition. We only used single channel EEG neurofeedback training in this pilot study. Future studies should integrate EEG connectivity analyses or EEG connectivity neurofeedback since phase synchronization will probably induce even stronger synaptic plasticity of selected brain regions of interest.

With respect to the above limitations, our longitudinal data require future replication in order to validate the relevance of our findings. Nevertheless, we could demonstrate stable long-term effects in a cohort of subjects under E-NFT and the data should be considered as an exploratory approach for a further hypothesis generation.

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Conflict of interest: The authors report no conflicts of interest.

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