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Improving episodic memory: Frontal-midline theta neurofeedback training increases source memory performance

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ABSTRACT

Cognitive and neurofeedback training (NFT) studies have demonstrated that training-induced alterations of frontal-midline (FM) theta activity (4–8 Hz) transfer to cognitive control processes. Given that FM theta oscillations are assumed to provide top-down control for episodic memory retrieval, especially for source retrieval, that is, accurate recollection of contextual details of prior episodes, the present study investigated whether FM theta NFT transfers to memory control processes. It was assessed (1) whether FM theta NFT improves source retrieval and modulates its underlying EEG characteristics and (2) whether this transfer extends over two posttests. Over seven NFT sessions, the training group who trained individual FM theta activity showed greater FM theta increase than an active control group who trained randomly chosen frequency bands. The training group showed better source retrieval in a posttraining session performed 13 days after NFT and their performance increases from pre- to both posttraining sessions were predicted by NFT theta increases. Thus, training-induced enhancement of memory control processes seems to protect newly formed memories from proactive interference of previously learned information. EEG analyses revealed that during pretest both groups showed source memory specific theta activity at frontal and parietal sites. Surprisingly, training-induced improvements in source retrieval tended to be accompanied by less prestimulus FM theta activity, which was predicted by NFT theta change for the training but not the control group, suggesting a more efficient use of memory control processes after training. The present findings provide unique evidence for the enhancement of memory control processes by FM theta NFT.

1. Introduction

The adult brain shows remarkable capacity for plasticity evidenced by transfer from working memory (WM) or multi-tasking training to other cognitive control processes (Anguera and Gazzaley, 2015; Kelly and Garavan, 2005; Lövdén et al., 2010). According to the overlap hypothesis of training transfer, successful training leads to transfer if both training and transfer tasks show functional and neural overlap, that is, the engagement of the same processing mechanisms and the activation of similar brain regions (Dahlin et al., 2008). Furthermore, these common brain substrates need to change as a function of training in order to result in training transfer (Lövdén et al., 2010). For instance, training gains of a multi-tasking training in elderly were shown to be accompanied by an increase of frontal-midline (FM) theta activity (4–8 Hz) that predicted transfer to performance in untrained attention and WM tasks (Anguera et al., 2013). Assuming that both functional and neural overlap are reflected in shared EEG dynamics, transfer should also occur if training alters task specific oscillatory activity. Indeed, enhancement of FM theta oscillations over several sessions of neurofeedback training (NFT), a form of operant conditioning that allows for training of oscillatory characteristics, resulted in transfer to cognitive control processes, such as task-switching, WM updating, and interference resolution (Enriquez-Geppert et al., 2014a; Wang and Hsieh, 2013). Thus far, training-induced performance increases have been accompanied by either a modulation of underlying FM theta activity or no such modulation (Enriquez-Geppert et al., 2014a). Although cognitive and neurofeedback training show transfer to cognitive control processes, it remains unclear whether training-induced upregulation of FM theta oscillations also transfers to memory control processes that are required for the coordination of encoding and retrieval in episodic memory.

Theta oscillations have been suggested to play a key role in memory control during episodic memory encoding and retrieval on both a representational and a processing level (Nyhus and Curran, 2010; Sauseng et al., 2010). On the representational level, theta-gamma coupling allows for the formation of memory representations by item-context binding, while on the processing level, theta phase coherence between frontal and posterior brain regions provides top-down con-

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trol over memory representations. Particularly, it has been suggested that the FM theta amplitude reflects the need for cognitive control that is then implemented over distant brain regions via theta phase synchronization (Cavanagh and Frank, 2014). Support for FM theta as a top-down control mechanism comes from studies demonstrating enhanced theta activity at both frontal and posterior sites for successful recollection of contextual details (Gruber et al., 2008; Guderian and Düzel, 2005; Klimesch et al., 2001a). In a similar vein, combined EEG-fMRI measurements showed that recollection-related theta-alpha oscillations are associated with increased connectivity of the hippocampus with the striatum and prefrontal cortex, two areas that have been related to top-down control (Herweg et al., 2016). Additionally, source localization of MEG activity demonstrated that successful encoding of memory associations was accompanied by increased theta phase coherence between the prefrontal cortex and the hippocampus, supporting an integrative role of theta oscillations (Backus et al., 2016). In a study by Addante et al. (2011), FM theta activity preceding a retrieval cue correlated with correct source but not item memory retrieval. Additionally, parietal theta activity obtained in a poststimulus interval was also indicative of correct source retrieval. Interestingly, frontal prestimulus theta activity correlated with parietal poststimulus theta activity, further supporting the view that FM theta oscillations exert top-down control for the retrieval of episodic memories reflected in parietal theta oscillations (Klimesch et al., 2008).

Even though ample evidence suggests that theta oscillations reflect a mechanism for memory control, the precise functional role of theta oscillations in episodic memory is still under debate (Guderian and Düzel, 2005; Hanslmayr and Staudigl, 2014; Hsieh and Ranganath, 2014; Klimesch et al., 2001b; Nyhus and Curran, 2010). Mainly three functional mechanisms of theta oscillations have been discussed in the literature. First, theta oscillations might reflect a retrieval mode that facilitates retrieval by activating brain regions important for retrieving episodic details, such as the frontal and parietal cortex (Klimesch et al., 2001a; Lepage et al., 2000). According to this view, prestimulus theta activity reflects the activation of task-relevant brain areas before the upcoming retrieval cue (Addante et al., 2011). Second, theta oscillations might support item-context binding by temporally ordering memory features via theta-gamma phase-amplitude coupling (Axmacher et al., 2010; Jensen and Lisman, 2005; Lisman and Jensen, 2013). More specifically, different features of episodic memories are suggested to be represented by single gamma amplitudes, which are nested onto a theta cycle in the order they are perceived (Hsieh and Ranganath, 2014; Nyhus and Curran, 2010; Roux and Uhlhaas, 2014; Sauseng et al., 2010). Consequently, one theta cycle binds multiple memory features into one coherent episodic memory representation with the theta phase coding the sequential order of the information. In support of this notion, enhanced theta-gamma cross-frequency coupling has not only been found within the hippocampus (Mormann et al., 2005), but also between frontal and parietal brain regions during episodic memory encoding (Friese et al., 2012) and retrieval (Köster et al., 2014). Third, another role of theta oscillations in episodic memory might be the coordination of inhibition strength over memory representations that compete for retrieval (Norman et al., 2005; Norman et al., 2006). According to this view, theta oscillations reflect varying levels of inhibition strength that coordinate the strengthening of target memories and the suppression of competitor representations. Supporting evidence comes from studies investigating the neural underpinnings of retrieval-induced forgetting, the phenomenon that selectively retrieving a memory impairs the recall of related memories (Hanslmayr et al., 2010; Staudigl et al., 2010). For instance, Hanslmayr et al. (2010) found enhanced theta activity in a competitive memory retrieval situation, in which competing irrelevant memories had to be suppressed, as compared to a noncompetitive retrieval situation. Interestingly, the increase in theta activity predicted the magnitude of retrieval-induced forgetting, supporting the idea that theta oscillations coordinate the inhibition of competitor memories. In another retrieval-induced forgetting study, theta activity that was initially increased during selective retrieval was shown to decrease after competitor representations had been successfully inhibited (Ferreira et al., 2014). Thus, interference due to competing retrieval seems to enhance control processes reflected in FM theta activity that support interference resolution by inhibiting competitor memories.

Direct modulation of FM theta activity underlying memory control processes offers a tool for investigating their causal relationship. One session of FM theta NFT applied directly after learning was shown to transfer to motor and item memory for up to one week as revealed by better recall of motor sequences and words that were learned before training (Rozengurt et al., 2016; Rozengurt et al., 2017). Even though these studies are interesting in that they suggest that NFT can improve consolidation of memory representations, it is still unclear whether FM theta NFT leads to enhancement of memory control processes that especially support source memory. In order to draw such conclusions about transfer to more general memory control processes, it is necessary to let participants learn and retrieve new information after NFT. Consequently, the present study investigates (1) whether source retrieval for items learned newly after NFT can be improved by enhancing FM theta oscillations via NFT and (2) whether this transfer is not only present one day after NFT, but persists to later learning and retrieval situations. Therefore, participants took part in seven NFT sessions in either an individual FM theta feedback training group or an active control group who trained session-wise randomly chosen frequency bands. Behavioral transfer to source retrieval and its underlying EEG characteristics were investigated in a pre-post design with a posttest one day after the last NFT session and a follow-up measurement 13 days after training. FM theta enhancement during NFT was expected to lead to better source memory performance at posttests for the training compared to the control group. Furthermore, the extent of FM theta increase during NFT should predict the degree of source memory performance enhancement from pretest to both posttests. Regarding the EEG characteristics underlying source retrieval, we first inspected both pre- and poststimulus oscillatory activity during pretest in order to obtain theta activity at frontal and parietal sites that has previously been associated with correct source retrieval. Concerning training-induced changes of EEG characteristics, we expected either increased or decreased prestimulus FM theta activity underlying memory control processes, implying either increased recruitment or a more efficient use of these processes after NFT.

2. Materials and methods

2.1. Participants

The sample consisted of 36 German volunteers who were recruited from Saarland University's student community. Participants were assigned to a training group (TG; $n = 17$, five male, $M_{\mathrm{TG}} = 22.65$ years, age range = 20–30 years) and an active control group (CG; $n = 18$, six male, $M_{\mathrm{CG}} = 23.33$ years, age range = 19–27 years) that were matched in sex, age, and study subject. One additional participant of the training group had to be excluded from analyses because of being an outlier in NFT theta increase as defined by the Tukey method with three interquartile ranges (Tukey, 1977). Prior to testing, participants conducted an online questionnaire inquiring the following characteristics considered important for recruitment. All recruited participants indicated to enjoy rollercoaster driving with a score > 4 on a 7-point Likert scale and both groups did not differ in their preference for rollercoaster driving ($M_{\mathrm{TG}} = 6.06$, $M_{\mathrm{CG}} = 6.22$; $t(33) = 0.54$, $p = .590$, $d = 0.19$). According to self-report, participants were healthy, had normal or corrected-to-normal vision, and no history of neurological or psychiatric disorders. Moreover, all participants were right-handed as indicated by the Edinburgh Handedness Inventory (Oldfield, 1971). Testing times were scheduled in accordance with each participant's chronotype based on the German version of the Morningness-Eveningness Questionnaire (D-

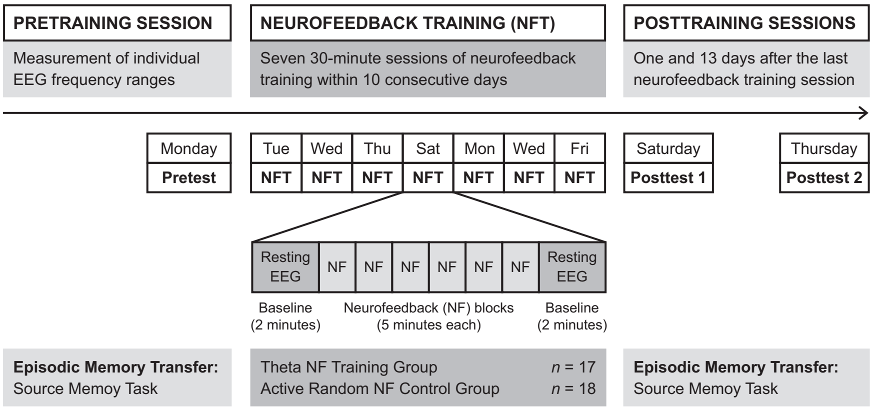

Fig. 1. Neurofeedback training schedule. Neurofeedback training consisted of seven neurofeedback sessions and transfer to source memory was investigated from one pretraining to two posttraining sessions. All sessions took place at the same fixed days for each participant.

MEQ; Griefahn et al., 2001). Written informed consent was provided prior to the experiment and participants were paid 8€ per hour in return for their participation. If desired, the payment was partially replaced by course credit. The experimental procedure was approved by the local ethics committee in accordance with the declaration of Helsinki.

2.2. Experimental design and data acquisition

Transfer effects from individual FM theta upregulation during NFT to episodic memory performance were assessed in a pre-post design (Fig. 1). Participants performed an intentional source memory task adapted from Addante et al. (2011) in a pretraining and two posttraining sessions. NFT for both groups took place on seven fixed days between the pre- and posttraining sessions. For all sessions, participants were seated comfortably in a dimly lit and quiet experimental room and experimental stimuli and NFT were presented on a Dell Computer with a Dell 24-inch monitor placed at a viewing distance of approximately 70 cm.

2.2.1. Source memory task

During encoding, 200 concrete German nouns were presented in four 50-item blocks that were counterbalanced for word length and frequency, using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, USA). Participants were asked to rate the animacy or pleasantness of the stimuli blockwise in an ABBA design. Therefore, the question “lebendig?” (German for “alive?”) or “angenehm?” (German for “pleasant?”) followed a 1000 ms fixation cross and a 1500 ms word presentation. The question remained until participants indicated their yes/no response with their left and right index fingers on the keys “C” and “M” on a conventional keyboard. During the approximately 30-minute retention phase, participants performed a delayed match to sample and a color Stroop task. In the following retrieval phase, the 200 previously learned words were presented intermixed with 100 new words in six blocks of 50 words each. After a 1000 ms fixation cross and a 1500 ms word presentation, participants were asked to indicate their item memory (old or new) on a 5-point Likert scale. If participants indicated the word as being old or rather old, they were subsequently asked to indicate their source memory (animacy or pleasantness) on a 5-point Likert scale. Left and right index and middle fingers were positioned on the number keys “1”, “2”, “4”, and “5”. The “don’t know” response on number key “3” was given with the right index finger. Response to key assignments were counterbalanced across participants but stayed fixed for each participant across all pre- and posttraining sessions.

2.2.2. Pre-/posttraining EEG recordings and processing

During the source memory task of pre- and posttests in the pre- and posttraining sessions, electroencephalographic (EEG) activity was recorded continuously with a sampling rate of 500 Hz from 32 Ag/AgCl electrodes using a Brain Amp EEG amplifier and Brain Vision Recorder software (Brain Products GmbH, Gilching, Germany). Scalp electrodes were mounted on a fitted cap according to the extended 10–20 system. Four additional electrodes placed at the outer canthi of the eyes and above and below the right eye were used to record the electrooculogram for eye movement detection. During the continuous EEG recording, electrode impedances were kept below 5 kΩ and signals were filtered with an online low-pass filter of 100 Hz. All electrodes were referenced to the left mastoid electrode during data acquisition and re-referenced offline to averaged mastoids.

Offline analysis of EEG signals was performed using Brain Vision Analyzer 2.1 software (Brain Products GmbH, Gilching, Germany). Raw data of both the encoding and retrieval phase was first inspected visually and artifact containing activity was removed manually in order to improve artifact correction by ICA decomposition. Data was then high-pass filtered at 0.5 Hz (48 dB/oct) and low-pass filtered at 40 Hz (48 dB/oct) before being re-referenced to linked mastoids. An infomax ICA was run to identify and remove components representing eye movements, such as blinks and saccades. Afterwards, the continuous EEG from encoding and retrieval was segmented from -1250 ms to 2400 ms around stimulus presentation. A baseline correction in the time domain from -200 ms to 0 ms prior to word presentation was applied as it was done in other time-frequency studies investigating prestimulus activity (e.g., Gruber et al., 2013). Finally, an automatic artifact rejection was applied with a maximal allowed voltage step of 30 μV/ms, a maximum-minimum difference of 100 μV, and an allowed amplitude of ± 60 μV. Segments with remaining artifacts were removed by hand. Trials were then divided into (1) correct item and source memory and (2) only correct item memory conditions.

For calculation of frequency power estimates, single trial activity from 1 Hz to 40 Hz was decomposed using a complex Morlet wavelet with 79 linear 0.5 Hz frequency steps and a time-frequency resolution indicated by a parameter c of 6. For both NFT and analyses of EEG characteristics during NFT and the transfer tasks, individual theta activity measures from the pretraining session were used. This was done because individual measures, which were also deployed by other FM theta NFT studies (Enriquez-Geppert et al., 2014a; Enriquez-Geppert et al., 2014b), account for between-subject variability in the dominant theta frequency peak and help to align FM theta activity measures during NFT and the transfer task. Based on previous findings of FM theta in episodic memory, especially its role for source retrieval (Hsieh and Ranganath, 2014), electrode Fz was selected for the derivation of individual FM theta activity. The individual FM theta range was defined as the individual FM theta peak (ITP) ± 1 Hz and determined between 4 and 8 Hz from EEG activity of the (1) correct item and source memory and (2) only correct item memory condition in the encoding phase of the pretraining session, conditions which are known to be reliably associated with enhanced theta activity (Friese et al., 2012; Osipova et al., 2006; Sederberg et al., 2003). Additionally, EEG measurements from a delayed matching to sample (DMTS) task, in which participants had

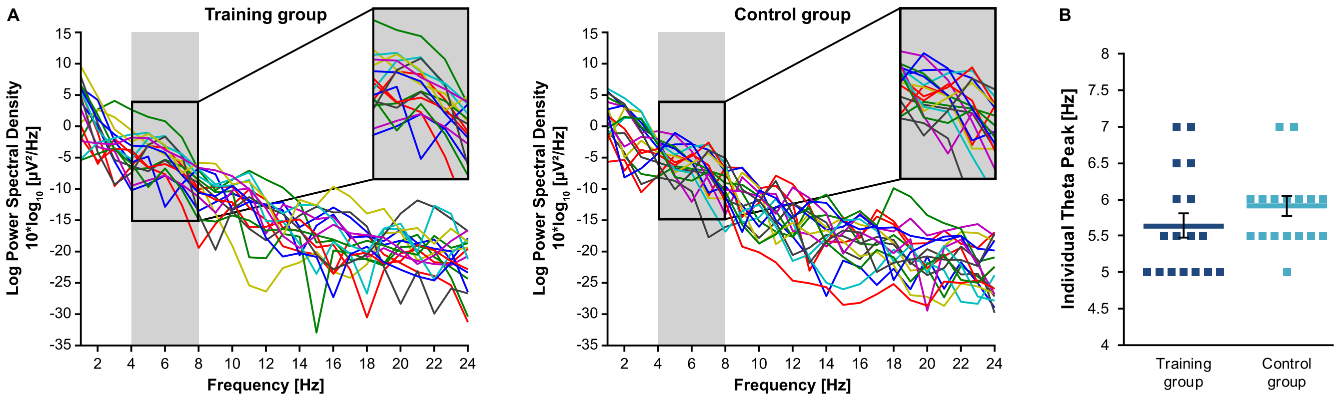

Fig. 2. Power spectra and mean individual theta peaks of the training and control group. (A) Individual power spectra of participants in the training and control group for the correct item and source memory condition of the source memory task during the pretraining session, one of the conditions from which individual theta peaks were extracted. Participants display different theta peaks within the theta range (4–8 Hz), which is marked by a gray bar. (B) The individual theta peaks ± 1 Hz that were derived from EEG measurements at pretest were used for the training of frontal-midline theta activity during NFT. Individual data points represent the number of participants with the respective theta peak, the solid lines indicate the group means, and error bars represent the standard error of the mean.

to manipulate and maintain visual stimuli during a retention period in order to compare them with an upcoming probe, were used for the derivation of individual FM theta activity. High task difficulty in this DMTS task has previously been associated with elevated FM theta activity in the retention interval (Berger et al., 2016; Eschmann et al., 2018; Griesmayr et al., 2014). The maximum theta power of each of the four conditions was averaged to achieve the mean ITP for every participant. Fig. 2A shows the individual power spectra separately for the training and control group in the correct item and source memory condition, a condition from which individual theta peaks for NFT were extracted. Participants of both groups show different frequency peaks within the 4–8 Hz theta range. Given that theta peaks in certain conditions may not be very distinctive for some participants, we calculated the mean ITP over several conditions of the transfer tasks. This has the advantage that a more robust measurement of individual theta activity is achieved, possibly increasing the likelihood of finding transfer effects. The derived mean ITPs of both the training and control group are depicted in Fig. 2B. Mean ITPs did not differ between training and control group ($M_{TG} = 5.65$, $M_{CG} = 5.92$; $t(33) = 1.22$, $p = .230$, $d = 0.43$).

For analyses of EEG characteristics in the source memory task in all pre- and posttraining sessions, EEG activity of the retrieval phase was separated in eight 200 ms epochs, resulting in three prestimulus (-600 to -400 ms, -400 to -200 ms, and -200 to 0 ms) and five poststimulus intervals (0–200 ms, 200–400 ms, 400–600 ms, 600–800 ms, and 800–1000 ms).

2.2.3. NFT protocol and processing

In order to train upregulation of theta activity by NFT, seven 30-minute neurofeedback sessions were conducted with a self-built feedback protocol using ProComp5 Infinity amplifier and BioGraph Infinity software (Thought Technology Ltd., Montreal, Canada). As in other FM theta NFT studies, individual FM theta (ITP ± 1 Hz) determined from the encoding phase of the pretraining session was used for theta NFT of the training group. As can be seen in Fig. 1, each of the seven neurofeedback training sessions consisted of six 5-minute blocks between which participants were able to take self-paced breaks and were asked about the strategy they used in the preceding block. Before and after training blocks a 2-minute fixation cross was presented in order to conduct start and end baselines of resting EEG activity. During NFT, electrophysiological activity was recorded with a 256 Hz sampling rate from an electrode placed at the Fz position (Rozengurt et al., 2016; Rozengurt et al., 2017; Wang and Hsieh, 2013) that was referenced and grounded by two electrodes at the earlobes. Electrode impedances were kept below 5 kΩ. Frequency bands for feedback generation were extracted from raw EEG with an infinite impulse response (IIR) filter and amplitude changes were calculated as the root mean square (RMS) over a sliding window of 256 data points (equals one second) with a 300 ms butterworth buffer. Feedback was presented visually in form of a rollercoaster animation, whose speed was controlled by the RMS of the to be trained frequency. Next to the rollercoaster animation, the speed of the rollercoaster was presented with a numerical speed indicator that depicted the percentage of the calculated RMS relative to the RMS value that was associated with the fixed maximum speed. Participants were asked to accelerate the rollercoaster speed for as fast and long as possible. While the training group trained their individual FM theta activity, the active control group received feedback to one of seven 2 Hz bands (10–12 Hz, 12–14 Hz, 14–16 Hz, 16–18 Hz, 18–20 Hz, 20–22 Hz, and 22–24 Hz) that was randomly chosen each session but was never used more than once (see Wang and Hsieh, 2013, for a similar procedure). In order to ensure a similar feedback increase between both groups, the maximum speed of the rollercoaster in the control group was adjusted to the rollercoaster speed in the training group. Depending on the amplitude of the randomly chosen frequency band and how advanced the training was, maximal feedback in the control group could be obtained with even smaller amplitudes. Both groups received the same list of strategies on how to speed up the rollercoaster (e.g., mental imagery, arithmetic operations, motor imagery) and were encouraged to find their own strategies within the variable strategy phase (first three neurofeedback sessions) and to use their preferred strategy in the constant strategy phase (remaining four training sessions). Two frequency bands (0.5–2 Hz and 43–59 Hz) were extracted in order to detect eye and muscle activity. Whenever an individually set threshold of those frequencies was exceeded, the rollercoaster stopped and an otherwise green light next to it lit up in red, indicating to the participant that there was an artifact. Participants did not know whether they belonged to the training or active control group, but were debriefed after the last posttraining session.

Offline analyses of the NFT data was conducted with Brain Vision Analyzer 2.1 software (Brain Products GmbH, Gilching, Germany). Raw data of training and baseline blocks were filtered with a 0.1–40 Hz bandpass filter (48 dB/oct) and segmented into 1-second intervals. Intervals with a voltage step greater than ±35 μV were discarded from further analyses in order to account for artefacts. Frequency analysis was performed with a fast Fourier transformation (FFT) with a 10% hamming window and normalization to overall power (1–24 Hz). Results were then averaged over all 1-second intervals for each block and each NFT session and amplitude values of individual theta (ITP ± 1 Hz), alpha (ITP + 3–5 Hz), and beta (ITP + 7–9 Hz) frequencies were extracted.

2.3. Data analyses

In order to analyze transfer effects, multiple regression analyses were used because they allow for controlling for pretest differences. In the analyses of training-induced changes in source memory performance and EEG characteristics, pretest measurements were included as an additional predictor of no further interest. However, this was not possible for the analyses of the NFT effect and its impact on transfer effects because NFT theta activity was measured repeatedly across seven training sessions. In these analyses, we controlled for inter-individual differences by using a within-session baseline-correction.

2.3.1. NFT effects

Individual FM theta amplitude during NFT was calculated as the percentage increase from the start baseline measurement of the respective session to the mean of the session's training blocks. By using this procedure, inter-individual differences in theta amplitude and differences between sessions due to measurement variability were accounted for. Training effects were analyzed with a repeated-measures ANOVA with the between-subject factor Group (TG vs. CG) and the within-subject factor Session (1–7). The same analyses were conducted with individual alpha and beta oscillations in order to investigate the specificity of FM theta NFT.

2.3.2. Behavioral transfer

NFT transfer effects to episodic memory were assessed with item and source memory performance as indicated by Pr scores (hits – false alarms) and the number of correct source judgments in the source memory task. Source memory is commonly calculated as the number of correct source judgments relative to all hits. However, a problem with this relative source memory measure is that it does not control for response bias in the item memory judgments that may differ across participants. Therefore, we also computed an absolute source memory score, that is, the number of correct source judgments relative to all old items, to control for influences of response bias. For reasons of greater transparency both source memory scores are reported. Behavioral transfer was investigated by two different sets of regression analyses. First, separate multiple regression analyses for both posttests with the predictor Group (TG vs. CG) assessed group differences in posttraining accuracy of the first and second posttest. To control for possible differences in pretraining performance, these multiple regression analyses included pretraining accuracy as an additional predictor. For these analyses, regression coefficients *b* and *t*-tests solely for the predictor of interest, namely Group, are reported. Multicollinearity effects might bias the results of the multiple regression analyses but tests of the variance inflation factor (VIF) showed that the behavioral data met the assumption of non-collinearity (all tolerance values > 0.98, all VIF values < 1.02). Second, the influence of participants' theta change during neurofeedback on their pre- to posttraining memory performance gain was investigated with linear regression analyses separately for each group. Participants' NFT theta change was calculated as the percentage increase from the variable (sessions 1–3) to the constant strategy phase (sessions 4–7) by using the individual FM theta amplitude relative to the respective session's start baseline. Behavioral performance gain was calculated as the percentage increase from pretraining to the respective posttraining session.

2.3.3. EEG characteristics of the transfer task

Based on the findings that theta activity at electrode Fz and P7 covaries with source memory performance (Addante et al., 2011), individual theta activity at these electrodes was analyzed. It was determined whether source memory specific FM and posterior theta activity at pretest was present irrespective of group. Therefore, individual theta activity in three prestimulus (-600 to -400 ms, -400 to -200 ms, and -200 to 0 ms) and five poststimulus time intervals of the retrieval phase (0–200 ms, 200–400 ms, 400–600 ms, 600–800 ms, 800–1000 ms) was tested with independent sample *t*-tests. Source memory specific theta activity was determined by subtracting the activity of the only correct item memory condition from the correct item and source memory condition (item and source correct – item only correct).

Consistent with the analyses of behavioral transfer, multiple regression analyses with the predictor Group (TG vs. CG) while accounting for pretraining activity were conducted separately for source memory specific theta activity of both posttests. For these analyses, the time intervals in which source memory specific theta activity was present at pretest were used. VIF tests indicated that the EEG data met the assumption of non-collinearity (all tolerance values > 0.87, all VIF values < 1.15). The influence of participants' NFT theta change on their pre- to posttest theta change was investigated with additional linear regression analyses similarly to the analyses of the behavioral transfer data. Therefore, FM theta change was calculated as the percentage change from pre- to the respective posttest.

For all analyses, the significance level was set to $\alpha = 0.05$ and if not indicated differently we used two-tailed tests. Whenever necessary, Greenhouse-Geisser correction was applied and adjusted *p*-values are provided. In order to correct for multiple comparisons of post-hoc tests, the false discovery rate (FDR) method was applied and adjusted *p*-values are given (Benjamini and Hochberg, 1995). For all regression analyses, univariate outliers were detected with the Tukey method using three interquartile ranges (Tukey, 1977) and bivariate outliers were calculated and excluded with the Mahalanobis distance method (Mahalanobis, 1936). Based on these outlier detection methods, seven participants were removed for one analysis each, one participant was excluded from two analyses, and two participants had to be removed for three analyses. Notably, none of the ten outliers had to be excluded from all analyses. Specifically, one participant of the control group had to be excluded from linear regression analysis investigating the influence of NFT theta change on absolute source memory performance change from pretest to the first posttest. For multiple regression analyses of EEG characteristics at the first posttest the following outliers were removed: one participant of the training group (-200 to 0 ms at Fz), one participant of the control group (400–600 ms at Fz and P7), and one participant of each group (600–800 ms at P7). For the same analyses at the second posttest one participant of the control group (-200 to 0 ms and 400–600 ms at Fz) and one participant of the training group (400–600 ms and 600–800 ms at P7) were discarded. In the linear regression analyses of FM theta activity with NFT theta change as predictor, two participants of the training group and one participant of the control group were removed for the pretest to the first posttest change and two control group participants were excluded for the pretest to the second posttest change.

3. Results

3.1. NFT effects

As depicted in Fig. 3A, individual FM theta activity differed between training and control group over the seven NFT sessions. A repeated-measures ANOVA revealed a significant main effect of Group ($F(1,33) = 6.31$, $p = .017$, $\eta_p^2 = 0.16$) and a significant Group by Session interaction ($F(6198) = 2.45$, $p = .026$, $\eta_p^2 = 0.07$) with a significant linear interaction contrast ($F(1,33) = 9.17$, $p = .005$, $\eta_p^2 = 0.22$), indicating that the difference in theta activity between both groups increased linearly over the course of the seven NFT sessions. Benjamini and Hochberg corrected one-tailed *t*-tests revealed that FM theta activity was significantly higher in the training group than in the control group in the constant strategy phase of NFT, that is, the fourth ($t(33) = 2.60$, $p = .014$, d = 0.91), fifth ($t(33) = 2.33$, $p = .029$, d = 0.81), sixth ($t(33) = 3.16$, $p = .007$, d = 1.10), and seventh NFT session ($t(33) = 2.41$, $p = .021$, d = 0.84). FM theta activity of both groups did not differ in the first three sessions (all *p*-values > .117). The linear interaction contrast was further confirmed by separate one-way repeated-measures ANOVAs for each group that showed a significant main effect of Session for the training group ($F(2.79,47.45) = 2.98$, $p = .044$, $\eta_p^2 = 0.15$) but not for the

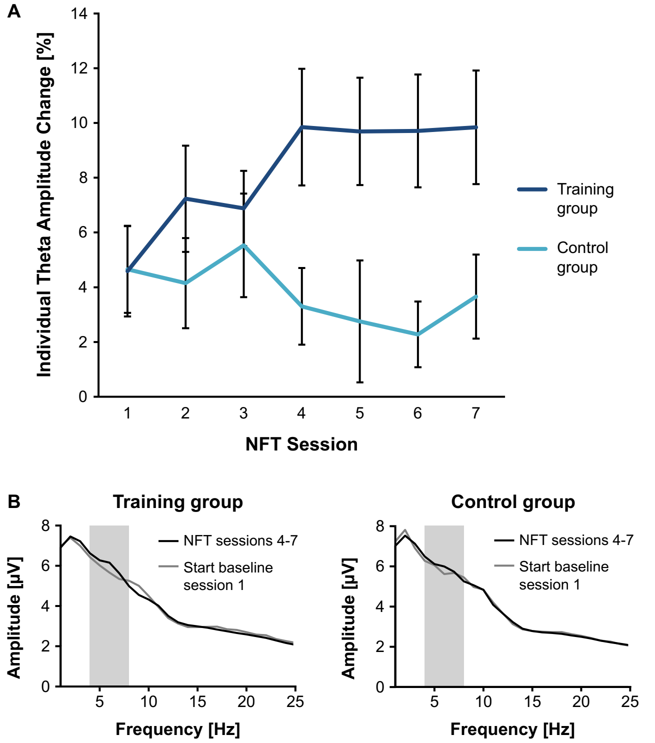

Fig. 3. Neurofeedback training results for the training and control group. (A) Increase of normalized individual theta amplitude during NFT relative to the resting EEG start baseline of the respective session. Error bars indicate standard error of the group means. (B) Power spectra of the first session's start baseline before any training took place relative to the power spectra of the constant strategy phase (NFT sessions 4–7), in which participants used their preferred strategy to upregulate their brain activity. Theta activity is marked by gray bars.

control group ($F(3.39,57.68) = 0.73$, $p = .552$, $\eta_p^2 = 0.04$), indicating that participants of the training group were able to enhance their FM theta amplitude linearly over the course of NFT whereas the control group was not able to do so. Repeated-measures ANOVAs investigating participants' individual alpha and beta activity did not reveal any significant main effects or interactions (all p-values > .063), suggesting that NFT selectively enhanced FM theta oscillations in the training group (Fig. 3B).

3.2. Behavioral transfer

Behavioral transfer effects from NFT training were investigated for the first and second posttraining session separately while controlling for pretraining performance (Fig. 4). Item memory was not significantly better for the training compared to the control group in the first ($b = 0.02$, $t(32) = 1.42$, $p = .082$, one-tailed) and second posttest ($b = 0.03$, $t(32) = 1.65$, $p = .055$, one-tailed), indicating that theta NFT did not induce a significantly greater increase in item memory performance in the training compared to the control group. In contrast, although absolute source memory performance did not differ between groups in the first posttest ($b = 0.03$, $t(32) = 1.46$, $p = .077$, one-tailed), performance of the training group was significantly better in the second posttest ($b = 0.04$, $t(32) = 1.81$, $p = .040$, one-tailed) conducted 13 days after the last NFT session. This finding demonstrates that the training group gave 4% more correct source memory responses in the second posttest compared to the control group, when pretest performance was controlled for. Results for relative source memory were not significant (all p-values > .093, one-tailed). These results indicate that theta NFT specifically enhanced source memory performance for the training compared to the active control group.[1]

Further linear regressions supported this claim by showing that NFT theta change predicted the gain in relative source memory performance from pretraining to the first ($b = 2.22$, $t(15) = 2.21$, $p = .043$) and second posttraining session for the training group ($b = 2.88$, $t(15) = 2.57$, $p = .021$) with NFT theta change explaining 24.5% and 30.6% of the variance in performance gain to the first posttest and to the second posttest, respectively (Fig. 5). As expected, the control group did not show a significant relationship of NFT theta change and memory accuracy gain from pre- to both posttraining sessions (all p-values > .216). Absolute source memory performance gains for both groups from pretraining to both posttraining sessions were not predicted by NFT theta change (all p-values > .054) as were item memory performance gains (all p-values > .104).[2]

3.3. EEG characteristics of the transfer task

3.3.1. Source memory specific theta activity during pretest

Using a priori t-tests we explored whether source memory specific theta activity (item and source correct – item only correct) was present at frontal and parietal measurement sites during pretest irrespective of group (Fig. 6). These t-tests revealed that source memory specific prestimulus FM theta activity measured at electrode Fz was significantly larger than zero in the -400 to -200 ms ($t(34) = 1.73$, $p = .046$, $d = 0.29$, one-tailed) and the -200 to 0 ms time interval ($t(34) = 1.74$, $p = .046$, $d = 0.29$, one-tailed). Moreover, source memory specific FM theta activity was present in the poststimulus time interval between 400–600 ms ($t(34) = 2.18$, $p = .018$, $d = 0.37$, one-tailed). Interestingly, source memory specific theta activity at posttest was also present at electrode P7, indicating that successful source memory retrieval was accompanied by both frontal and parietal theta activity. Parietal theta activity was present in the poststimulus time intervals of 400–600 ms ($t(34) = 2.18$, $p = .018$, $d = 0.37$, one-tailed) and 600–800 ms ($t(34) = 2.18$, $p = .018$, $d = 0.37$, one-tailed). In all other time intervals during pretest, theta activity did not differ significantly from zero at both measurement sites (all p-values > .056, one-tailed). Theta activity did not differ between training and control group in all time intervals, in which source memory specific theta activity was present (all p-values > .093).

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[1] Three participants of the training group and one participant of the control group showed chance performance at one or both posttests, indicating that they might not have performed the task as instructed after training. By excluding more chance performers from the training than the control group in the analyses we might have biased our analyses towards finding group differences in source memory performance. Therefore, chance performers were included in the initial analyses. However, to provide a more comprehensive picture of the transfer effects and to show that our results are reliable across several analysis techniques, we report the results of the behavioral analyses without chance performers here. These analyses revealed that relative and absolute source memory performance was better for the training ($n = 14$) compared to the control group ($n = 17$) at both posttests. For relative source memory, the training group had better performance than the control group in the first ($b = 0.04$, $t(28) = 1.75$, $p = .045$, one-tailed) and second posttest ($b = 0.07$, $t(28) = 2.83$, $p = .004$, one-tailed). Similarly, the training group showed better absolute source memory performance in the first ($b = 0.06$, $t(28) = 1.94$, $p = .031$, one-tailed) and second posttest ($b = 0.11$, $t(28) = 2.89$, $p = .004$, one-tailed).

[2] Even though between-group differences in item memory at both posttests and linear regressions with NFT theta change as a predictor were not significant when performance was measured by Pr scores, it could still be the case that analyses with either hit or false alarm rates may have revealed significant results. However, the same pattern of results was found when hits and false alarms were analyzed separately with no significant group differences at both posttests (all p-values > .058, one-tailed) and no significant prediction of pre- to posttest changes by NFT theta change for both groups (all p-values > .177).

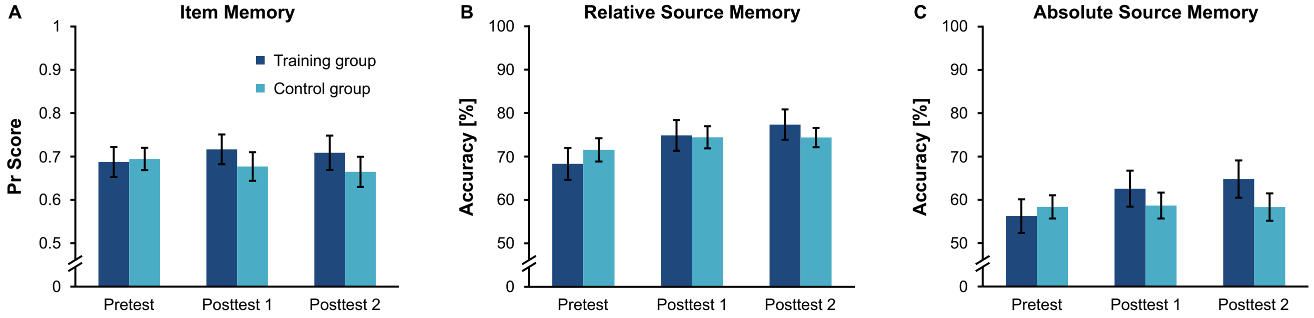

Fig. 4. Behavioral results of (A) item memory, (B) relative source memory, and (C) absolute source memory at pretest and the two posttests displayed separately for training and control group. Error bars indicate standard error of the group means. The training group showed better absolute source memory performance than the control group in the second posttest.

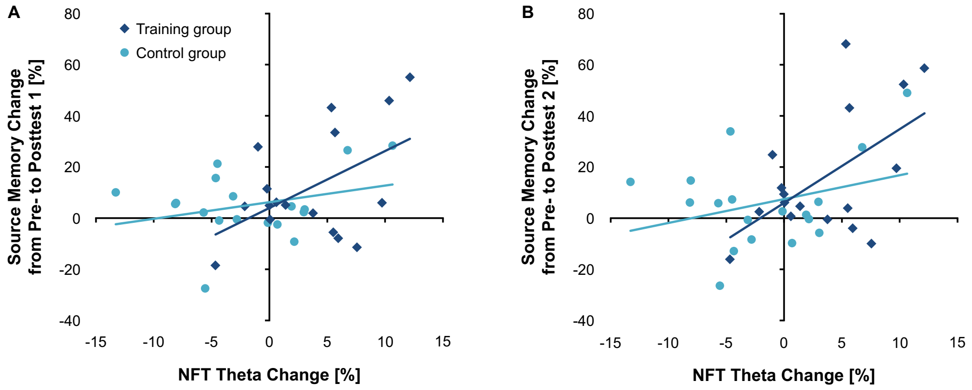

Fig. 5. NFT effects on behavioral transfer for the training and control group. NFT theta change significantly predicted the change of relative source memory from pretest to (A) the first and (B) the second posttest for the training but not for the control group.

3.3.2. Training-induced changes in EEG characteristics

In order to determine training-induced changes in source memory specific theta activity, group differences at both posttests were analyzed with multiple regression analyses that controlled for pretest activity (Fig. 7A). In these analyses, source memory specific FM and posterior theta activity was used only in those intervals, in which theta activity was significantly present during retrieval at pretest, in order to minimize the possibility of false positive findings. Multiple regression analyses revealed a non-significant trend of prestimulus FM theta reduction for the training compared to the control group in the -400 ms to -200 ms time interval of the second posttest ($b = 1.69$, $t(32) = 1.73$, $p = .093$). Group differences for all other prestimulus and poststimulus time intervals at both posttests were neither significant for FM theta activity (all p-values > .289) nor for posterior theta activity (all p-values > .166). The influence of NFT theta change on FM theta activity in the source memory task was investigated in the -400 to -200 ms prestimulus time interval, in which theta activity has previously been associated with memory control processes (Addante et al., 2011). Therefore, linear regression analyses with the percentage change of theta activity from pre- to the first and second posttest as dependent variables were conducted separately for both groups. As shown in Fig. 7B, NFT theta change significantly predicted FM theta change in the -400 to -200 ms time interval from pre- to the second posttest for the training group ($b = 17.80$, $t(15) = 2.16$, $p = .047$), explaining 23.7% of the variance of theta decrease. There was no corresponding effect for the control group ($b = 5.57$, $t(14) = 0.60$, $p = .557$). NFT theta change did not predict FM theta change from pre- to the first posttest for both groups (p-values > .450). These findings indicate that FM theta NFT induced a decrease in source memory specific FM theta activity during the prestimulus interval of the retrieval phase in the second posttest. Together with the better source retrieval of the training group in the second posttest these results may suggest a more efficient use of memory control processes after training.

4. Discussion

Cognitive and neurofeedback training studies have shown transfer to cognitive control processes that are associated with FM theta oscillations (Anguera et al., 2013; Enriquez-Geppert et al., 2014a; Wang and Hsieh, 2013). Given that FM theta activity also provides top-down control for episodic memory retrieval (Klimesch et al., 2008; Nyhus and Curran, 2010; Sauseng et al., 2010), especially for source retrieval (Addante et al., 2011), the present study investigated whether FM theta upregulation also transfers to memory control processes. More specifically, we assessed whether FM theta NFT transfers to source memory performance for information newly learned after training and its underlying EEG characteristics. Additionally, we explored the time course of this training transfer (Fig. 1). As expected, seven NFT sessions of individually defined theta band ranges led to FM theta increase in the training group compared to an active control group that was matched on all relevant aspects but received feedback for frequency bands that were randomly chosen for each session (Fig. 3). This finding adds to a growing body of studies showing that FM theta oscillations can be trained with neurofeedback (Enriquez-Geppert et al., 2014a; Enriquez-Geppert et al., 2014b; Reis et al., 2016; Rozengurt et al., 2016; Rozengurt et al., 2017; Wang and Hsieh, 2013). Of note, NFT theta changes were not accompanied by changes in neighboring frequency bands, such as individual alpha and beta activity, indicating that oscillatory changes were specific to the trained activity (Gruzelier, 2014). Interestingly, theta NFT improved source memory performance at the second posttest as revealed by higher absolute source memory performance of the training compared to the control group (Fig. 4). Linear regression analyses revealed that the gain in source memory performance from pretest to both posttests was predicted by the individual NFT theta enhancement for the training but not the control group (Fig. 5). These results reveal that source memory performance can be improved by enhancing FM theta oscillations

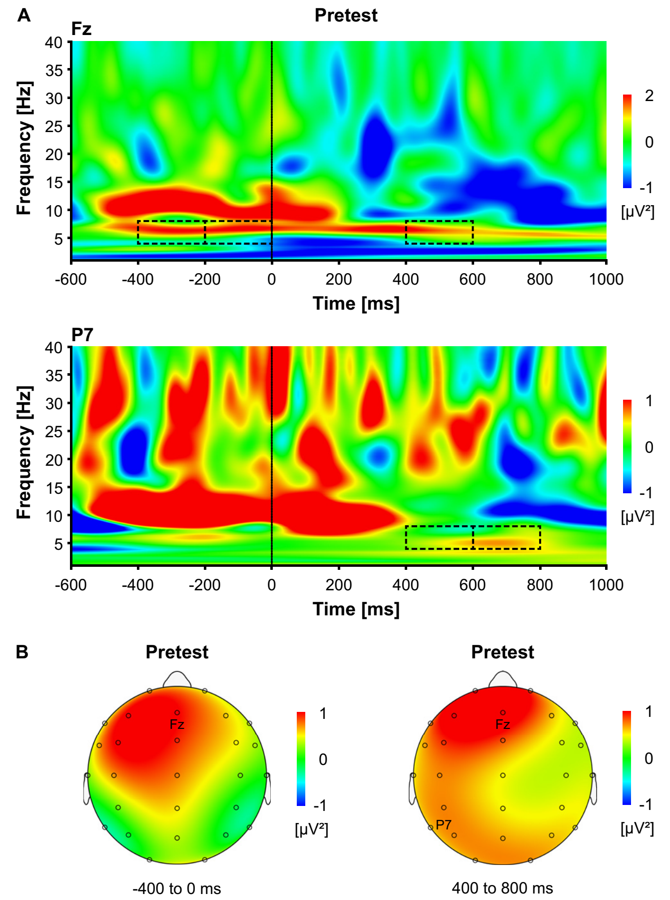

Fig. 6. Electrophysiological characteristics of the source memory task at pretest. (A) Time-frequency plots of source memory specific frontal-midline (FM) and posterior theta activity during retrieval at electrode Fz and P7 averaged over all participants of both groups. Time intervals of significant individual theta activity are marked by black dashed squares. (B) Topographical maps of source memory specific individual theta power from -400 to 0 ms and 400–800 ms during retrieval averaged over all participants of both groups.

with neurofeedback and that the amount of FM theta NFT success predicts the performance benefit. By assessing how NFT transfers to source memory, the present study extends previous findings of NFT transfer to motor and item memory (Rozengurt et al., 2016; Rozengurt et al., 2017). As these FM theta NFT studies tested memory for movements and words that were learned immediately before NFT, they solely allow conclusions about the consolidation of previously learned information. In contrast, the present study is the first to demonstrate that FM theta upregulation transfers to source retrieval of newly learned information and, thereby, provides unique evidence that NFT can enhance memory control processes needed for the retrieval of episodic memories.

Contrary to our initial expectations, theta NFT showed transfer to source memory performance mainly in the second posttest, indicating that performance differences between groups were most pronounced not one but 13 days after the last NFT session. An explanation for these temporally specific transfer effects can be derived from the characteristics of the source memory task. Since participants learned new words and their respective source in every of the pre- and posttraining sessions, the amount of already learned information increased with each of the transfer sessions, leading to greater proactive interference in the second posttest than in preceding sessions. Proactive interference refers to the phenomenon that previously acquired knowledge impairs the ability to remember newly learned information. Our study design has high similarity with the classical proactive interference paradigm. In this paradigm, usually several lists of word pairs are learned whereby the same cue words are associated with different words in each list (Underwood, 1957). Reduced memory accuracy is found for words that are associated with the same cue word or as in the present study with the same source information (Blumenfeld and Ranganath, 2007). Consequently, memory for more recent events decreases as the number of prior memories increases. The finding that NFT transfer effects were present in the second posttest, in which older memories from several sessions (pretraining and first posttraing session) interfered with the retrieval of more recent memories, might be explained by the particularly high demands on memory control processes to counteract proactive interference in this late posttraining session. This would suggest that NFT of FM theta oscillations helps to prevent interference and in turn improves source memory performance (Nyhus and Curran, 2010; Sauseng et al., 2010). An objection against this interpretation would be that memory performance should decrease particularly for the control group with increasing interference from pretest to the first and second posttest, which was not the case in the present study. However, repeated task performance over several sessions may have compensated for the deteriorating effects of proactive interference on memory performance.

Analyses of EEG characteristics during pretest revealed the presence of source memory specific prestimulus FM theta activity (Fig. 6) that has previously been shown to correlate with source memory performance (Addante et al., 2011). Moreover, source memory specific poststimulus theta activity was present at frontal and posterior recording sites, which is in line with studies associating frontal and posterior theta activity with successful recollection of contextual details (Gruber et al., 2008; Guderian and Düzel, 2005; Klimesch et al., 2001a). Interestingly, poststimulus theta activity did not change as a function of training. Analyses of training-induced changes in prestimulus FM theta activity showed only a trend of less theta activity for the training group in the second posttest and, thus, has to be interpreted carefully (Fig. 7A). Nevertheless, NFT theta changes significantly predicted prestimulus FM theta decrease

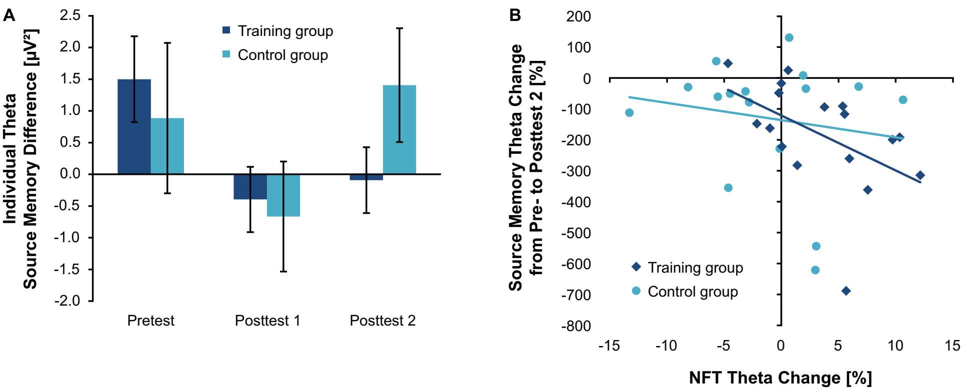

Fig. 7. NFT effects on electrophysiological characteristics for the training and control group. (A) Source memory specific prestimulus theta power from -400 to -200 ms during retrieval at pretest, first posttest, and second posttest at electrode Fz shown separately for training and control group. Error bars indicate standard error of the group means. The training group tended to show less theta activity than the control group in the second posttest. (B) NFT theta change significantly predicted the change of source memory specific FM theta from -400 to -200 ms during retrieval from pretest to the second posttest for the training but not for the control group.

from pre- to the second posttest for the training but not the control group (Fig. 7B). This finding might be surprising since cognitive training studies examining transfer to cognitive control showed increases in FM theta activity associated with behavioral transfer (Anguera et al., 2013). However, decreased neural activation associated with performance increases after cognitive training are reported frequently in brain imaging studies (Debaere et al, 2004; Schneiders et al., 2011) and are interpreted to be part of a redistribution of functional activity after training (Kelly and Garavan, 2005). By this view, activation decreases in areas important for attention and cognitive control, such as the anterior cingulate cortex (ACC), reflect a more efficient recruitment of brain regions needed for successful task performance. Given that the dorsal ACC, also referred to as midcingulate cortex (MCC), is a source region of FM theta activity (Cavanagh and Frank, 2014), it is conceivable that the simultaneous decrease in theta activity and performance increase in the training group at the second posttest reflect a higher efficiency of memory control processes as a function of NFT. In line with this interpretation, theta activity decreases during successful memory performance have been suggested to be accompanied by increased inter-regional theta coherence (Herweg et al., 2019). If FM theta indeed reflects the need for cognitive control (Cavanagh and Frank, 2014), this need for cognitive control might be diminished after FM theta NFT due to a more efficient implementation of these cognitive control processes through a possibly enhanced phase synchronization.[3]

Given that upregulation of theta activity during NFT predicted source memory increases and FM theta decreases in the transfer task, the present study gives new insights into the functional mechanisms of theta oscillations. First, theta upregulation might have improved the adaptation of a neuro-cognitive state that supports retrieval of all memories irrespective of their context, similar to the idea of retrieval mode (Klimesch et al., 2001a; Lepage et al., 2000). However, if this would have been the case, item memory performance should have profited from theta NFT to a similar extent and memory improvements should have been clearly present in both posttraining sessions and not mainly in the second one. Second, in the present study, binding of items with their source context (animacy or pleasantness) and during later sessions also temporal context (session in which item-source association was learned), was important to achieve good source memory performance. Reinstating aspects of the encoding context, that is, which items were associated with which source in which encoding session, may have been beneficial for correct source retrieval upon presentation of the test cue. In particular, in situations in which the risk for confusing words from different encoding and retrieval phases, that is, different temporal contexts, was high, upregulation of FM theta amplitudes during training might have enabled more precise – especially temporal – context reinstatement which in turn led to a better recollection of the learned item-source associations (Hsieh and Ranganath, 2014; Nyhus and Curran, 2010). Supporting this latter assumption, several studies showed that FM theta oscillations are especially pronounced when temporal order information as compared to item or spatial information had to be maintained in working memory (Hsieh et al., 2011; Roberts et al., 2014). In accordance, theta oscillations were suggested to also code temporal context information of episodic memories (Heusser et al., 2016; Jensen and Lisman, 2005). However, in the present study, memory performance increases in the transfer task were accompanied by source memory specific theta decreases and not by increases of FM theta activity. This apparent inconsistency might be reconciled by taking studies into account that show that decreased theta activity can be associated with increased memory performance (Burke et al., 2013; Crespo-García et al., 2016; Greenberg et al., 2015). Based on these studies, it has been proposed that reduced theta activity is a marker of mechanisms that down-regulate noisy inputs and up-regulate task-relevant information, leading to more precise representations of memory contents (Herweg et al., 2019). This is thought to be achieved by information-richer temporal phase coding that enables more precise stimulus-specific neural firing (Hanslmayr et al., 2016). According to this view, training-induced decreases of theta activity in the present study allowed for a more precise neural coding and reactivation of the learned information by decreasing synchronized unit activity or increasing neural firing rates. Moreover, it is also conceivable that training-induced decrease of source memory specific FM theta activity was accompanied by enhanced theta-gamma coupling enabling item-context binding via temporal ordering. Thus, even though theta amplitudes were smaller for the training group after NFT, they allowed for enhanced item-context binding (Köster et al., 2014) and, consequently, for a better reinstatement of the respective temporal context information that alleviated episodic memory retrieval. Third, theta NFT could have supported protection from interference by coordinating inhibition over competing memory representations (Norman et al., 2005; Norman et al., 2006). This inhibition account proposes that theta oscillations reflect varying levels of inhibition strength that influence retrieval competition in a way that target representations are strengthened and related memories that compete for retrieval are suppressed. In support of this proposal, FM theta activity seems to reflect the time course of interference with increased theta activity during selective retrieval and decreases after competitor representations had been suppressed (Ferreira et al., 2014). In the present study, interference arose from competition of source and temporal contexts associated with previously and newly learned information. Consequently, theta NFT might have protected participants of the training group from this interference by providing greater inhibition of interfering context representations of previous and current sessions, resulting in better protection from these interfering memories and, thus, in better source memory performance. This interpretation is in line with the view that theta decreases represent the upregulation of mechanisms that inhibit irrelevant information while facilitating task relevant information (Hanslmayr et al., 2016; Herweg et al., 2019). Decreased source memory specific FM theta activity might reflect the more efficient strengthening of target memory representations and inhibition of competitor representations, resulting in increased source memory performance. Altogether, the findings of the present study suggest that FM theta oscillations either provide temporal and encoding context information or coordination of inhibition strength over competing memory representations. Notably, both functional roles of FM theta oscillations are not necessarily mutually exclusive. Although FM theta oscillations have been assumed to reflect a general neural mechanism for cognitive control (Cavanagh and Frank, 2014), it has been proposed that it might be oversimplifying to assume one functional role for FM theta activity (Hsieh and Ranganath, 2014).

In the present study, behavioral transfer to both posttests and theta changes from pre- to both posttraining sessions were predicted by individual NFT theta changes, demonstrating the importance of taking individual differences into account for determining the efficiency of NFT. Even if individually estimated frequency bands are trained, some participants have shown to be non-responsive to NFT (Enriquez-Geppert et al.,

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[3] As pointed out by a reviewer, it is conceivable that resting-state theta activity after training changed on the basis of NFT. FM theta upregulation during training may have resulted in either increased or decreased resting-state theta activity in the end baseline. In consequence, the new set-point for resting-state theta activity might have biased the training-induced changes of FM theta activity during the source memory task in the posttraining sessions. An increased end baseline may have reduced the possibility for finding further theta increases in the transfer task. In contrast, a decreased end baseline may have led to theta decreases in the source memory task. To test whether resting-state EEG activity changed based on NFT, we conducted a repeated-measures ANOVA with the factors Baseline (start vs. end) and Session (1-7) for the training group. Neither the main effects of Baseline and Session nor the interaction Baseline by Session were significant (all p-values $> .109$). Thus, there was no evidence for significant changes of resting-state theta activity from start to end baseline and across all training sessions. We conclude that training-induced decreases in source memory specific theta activity are not caused by baseline activity changes but indeed show a more efficient use of theta activity of the training group during the source memory task.

2014b; Hanslmayr et al., 2005; Weber et al., 2011) and it has been argued that small MCC volumes contribute to the non-responsiveness to NFT (Enriquez-Geppert et al., 2013; Ninaus et al., 2015). Interestingly, older participants show small FM theta amplitudes that are not related to small MCC volumes but are associated with cognitive decline instead (Kardos et al., 2014). Thus, given their structurally intact MCC older participants might be responsive to FM theta NFT similarly to younger participants and neurofeedback might be a helpful tool to counteract cognitive decline in elderly. In support of this view, cognitive training and NFT studies with older participants have shown that FM theta activity can be modulated with training even in old age and that theta enhancement is associated with transfer to cognitive control processes (Anguera et al., 2013; Wang and Hsieh, 2013; Reis et al., 2016). As the present study showed transfer to memory control processes which are beneficial for associative memory retrieval, particularly source memory performance, FM theta NFT might be helpful in improving older adults' associative memory deficit (Naveh-Benjamin et al., 2003).

In conclusion, the present study to our knowledge is the first that shows transfer from FM theta NFT to source memory retrieval for information newly learned after training, demonstrating that neurofeedback can be used to improve memory control processes. The present findings are consistent with the view that training of individually estimated FM theta oscillations leads to protection from proactive interference especially in situations with a high risk of interference from previously acquired memories. Even though the exact mechanisms by which this protection from interference is achieved have to be unveiled, it is not unlikely that training-induced source memory improvements are accomplished by greater precision of temporal context reinstatement (Hsieh and Ranganath, 2014) or of inhibition of irrelevant memory representations during competitive memory retrieval (Norman et al., 2005; Norman et al., 2006). Consequently, individual FM theta NFT constitutes an intervention technique for memory enhancement in young adults with potential relevance for treatment of memory decline in old age.

Credit author statement

Kathrin C. J. Eschmann: conceptualization, methodology, software, validation, analysis, investigation, data curation, writing – original draft, visualization, project administration. **Regine Bader:** conceptualization, methodology, software, writing – review and editing. **Axel Mecklinger:** conceptualization, methodology, writing – review and editing, supervision

Declaration of competing interest

The authors declare no competing financial interests.

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