



RESEARCH ARTICLE

Endogenously generated gamma-band oscillations in early visual cortex: A neurofeedback study

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Abstract

Human subjects were trained with neurofeedback (NFB) to enhance the power of narrow-band gamma oscillations in circumscribed regions of early visual cortex. To select the region and the oscillation frequency for NFB training, gamma oscillations were induced with locally presented drifting gratings. The source and frequency of these induced oscillations were determined using beamforming methods. During NFB training the power of narrow band gamma oscillations was continuously extracted from this source with online beamforming and converted into the pitch of a tone signal. We found that seven out of ten subjects were able to selectively increase the amplitude of gamma oscillations in the absence of visual stimulation. One subject however failed completely and two subjects succeeded to manipulate the feedback signal by contraction of muscles. In all subjects the attempts to enhance visual gamma oscillations were associated with an increase of beta oscillations over precentral/frontal regions. Only successful subjects exhibited an additional marked increase of theta oscillations over precentral/prefrontal and temporal regions whereas unsuccessful subjects showed an increase of alpha band oscillations over occipital regions. We argue that spatially confined networks in early visual cortex can be entrained to engage in narrow band gamma oscillations not only by visual stimuli but also by top down signals. We interpret the concomitant increase in beta oscillations as indication for an engagement of the fronto-parietal attention network and the increase of theta oscillations as a correlate of imagery. Our finding support the application of NFB in disease conditions associated with impaired gamma synchronization.

KEYWORDS

human, imagery, neurofeedback, visual cortex, visual gamma oscillation

1 | INTRODUCTION

Oscillatory modulation and synchronization of neuronal responses in the gamma- frequency band (30–90 Hz) has first been described in the early visual cortex of cats (Gray & Singer, 1989) and subsequently identified as a ubiquitous phenomenon in most cortical and several subcortical structures of a variety of species including humans (Buzsáki, 2011; Fries, Roelfsema, Engel, König, & Singer, 1997; Fries, 2009; Greenhouse, Noah, Maddock, & Ivry, 2016; Hoogenboom, Schoffelen, Oostenveld, Parkes, & Fries, 2006; Moser et al., 2010; for reviews see Singer, 1999; Buzsáki, Logothetis, & Singer, 2013). When groups of neurons engage in gamma oscillations these undergo periodic and synchronized changes of excitability (Fries, Nikolić, & Singer, 2007; Sohal, 2016). Phases of enhanced excitability alternate with phases of strong inhibition. This restricts the interval during which cells are

susceptible to excitatory input and able to emit spikes to a narrow window of opportunity. This has two important consequences: First, the resulting synchronization of discharges increases their impact on downstream targets (Bruno & Sakmann, 2006) and second, exchange of information between coupled groups of oscillating neurons becomes dependent on the frequency and phase of the respective oscillations. Neurons oscillating in antiphase are functionally decoupled even if anatomically connected because their discharges always fall in the refractory period of the respective receiving neuron while neurons oscillating in phase can drive one another and exchange information very effectively (Bastos et al., 2015; Fries, Womelsdorf, Oostenveld, & Desimone, 2008; Schoffelen, Oostenveld, & Fries, 2005) (for review see (Fries, 2005)). Because of these functions gamma oscillations and their synchronization have been assigned a role in a large variety of processes: feature binding and assembly formation (Singer & Gray, 1995; Fell

et al., 2001), gating of signal transmission and dynamic configuration of functional networks (Baldauf & Desimone, 2014; Bosman et al., 2012; Munk, Roelfsema, König, Engel, & Singer, 1996), polysensory integration (Mishra, Martinez, Sejnowski, & Hillyard, 2007; Yuval-Greenberg & Deouell, 2007), maintenance and readout of working memory (Kaiser, Ripper, Birbaumer, & Lutzenberger, 2003; Lundqvist et al., 2016; Roux, Wibral, Mohr, Singer, & Uhlhaas, 2012), activation of predictions (Bauer, Stenner, Friston, & Dolan, 2014; Brodski, Paasch, Helbling, & Wibral, 2015) and selective attention (Fries, Reynolds, Rorie, & Desimone, 2001b; Siegel, Donner, Oostenveld, Fries, & Engel, 2008). Evidence also indicates that certain diseases such as autism spectrum disorder, schizophrenia, Alzheimer's and Parkinson are associated with abnormalities of gamma oscillations and their synchronization (Spencer, Niznikiewicz, Nestor, Shenton, & McCarley, 2009; Uhlhaas & Singer, 2006, 2010). Because of the association of gamma oscillations with multiple cognitive and executive functions it is of interest to find out to which extent they are subject to volitional control. Several studies have documented that stimulus induced gamma oscillations depend on central states (Herculano-Houzel, Munk, Neuenschwander, & Singer, 1999) and can be modulated by expectancy and attention (Fries, Reynolds, Rorie, & Desimone, 2001a; Gregoriou, Gotts, & Desimone, 2012; Siegel et al., 2008; Lima et al. 2011). Gamma oscillations closely resembling those induced with sensory stimulation can also be entrained with optogenetic stimulation (Kim, Ährlund-Richter, Wang, Deisseroth, & Carlén, 2016; Siegle, Pritchett, & Moore, 2014) or non-invasively with transcranial magnetic or direct current stimulation (Barr et al., 2009). However, it is less clear, whether they are susceptible to volitional control.

Using neurofeedback (NFB) techniques evidence has been obtained that subjects are able to modify the power of brain oscillations in selected frequency bands. However, most of the studies have concentrated on frequencies below the gamma band (Gruzelier, 2014; Kamiya & Nowlis, 1970; Nan et al., 2012; Staufenbiel, Brouwer, Keizer, & van Wouwe, 2014). The most direct evidence for a modulation of gamma power that was both frequency and site specific has been obtained in a NFB study with monkeys by Engelhard et al., (2013). In this experiment the power of gamma oscillations assessed from local field potentials (LFPs) recorded with electrodes located in the motor cortex was converted in a visual stimulus—a moving cursor—and the reward was made contingent with the movement indicating power increases. In this setting monkeys were able to enhance the power of the gamma band selected for feedback and this enhancement was confined to the cortical site from which the feedback signal was derived.

Attempts to modify gamma band oscillations in human subjects with NFB techniques were mainly aimed at investigating ensuing alterations of cognitive functions (Keizer, Verment, & Hommel, 2010; Keizer, Verschoor, Verment, & Hommel, 2010; Salari, Büchel, & Rose, 2014; Staufenbiel et al., 2014) and hence less emphasis was put on the localization of the sources of activity and the frequency specificity of the NFB effects.

The goal of the present study was to examine with the NFB method to which extent human subjects are able to generate or enhance gamma oscillations and to confine this enhancement to a

narrow frequency band and to a predefined region of the cerebral cortex. To this end we derived the feedback signal from high density magnetoencephalographic (MEG) recordings to minimize spatial smearing due to volume conduction (Sato, Balish, & Muratore, 1991), restricted the source of the signal used for feedback by online beamforming to a small region of the visual cortex, selected as the NFB target frequency the peak frequency of gamma oscillations induced in the selected region with light stimuli, subtracted the power of frequencies flanking the selected frequency from the source activity to encourage enhancement of narrow band power and then converted the power of the pre-processed signal into the pitch of a tone, asking the subjects to first obtain control over the pitch and then to enhance it. During this phase, no light stimuli were presented because we were interested in the ability of subjects to generate gamma oscillations rather than to just modulate the amplitude of stimulus induced oscillations. In order to obtain further indications on the specificity of NFB effects we performed in addition a whole brain analysis of oscillations and their modifications across a wide spectrum of frequencies and performed extensive controls for artifacts caused by non-neuronal activity. These controls proved to be absolutely crucial because muscle contractions are associated with electrical potentials whose spectral composition overlaps with that of gamma oscillations (Hipp & Siegel, 2013; Muthukumaraswamy & Singh, 2013) and it turned out that some subjects actually attempted to modulate the feedback signal by differential activation of neck and head muscles. Unlike in off-line processing (Gross et al., 2001), muscle artifacts are difficult to eliminate online as would be required in the NFB setting.

2 | MATERIAL AND METHODS

2.1 | Subjects

The NFB experiments were performed with 10 healthy subjects (five females, age range 19–32, mean: 23.1) who had no metal implants and normal or corrected-to-normal vision (with contact lenses or MEG compatible glasses). Subjects received oral and written information about the study, gave written consent and were remunerated with 10 Euro per hour. All experiments were approved by the local ethics committee (Johann-Wolfgang-Goethe University, Frankfurt am Main, Germany).

2.2 | Data acquisition

MEG data acquisition was performed according to commonly accepted guidelines (Gross et al., 2013) with a whole-head MEG system containing 275 axial gradiometers (SQUID's) (VSM MedTech, Port Coquitlam, Canada) that was placed in a magnetically shielded chamber (Vacuum-schmelze Hanau) at the MEG Lab of the University of Frankfurt. Data were recorded in a synthetic third order gradiometer configuration with a sampling rate of 1,200 Hz and band pass filtered from 0.1 to 300 Hz with a fourth-order Butterworth filter. Visual stimuli were back-projected onto a translucent screen placed at a distance of 53 cm

from the subjects' eye plane with a video beamer (vertical refresh rate of 60 Hz) located outside the MEG chamber.

For the source reconstruction structural MR images were acquired using a 3-T Siemens Allegra and a 3-T Siemens Trio scanner (Siemens Medical Solutions, Erlangen, Germany) with 4-channel head coils and gradient strength of 40 mT/m. Anatomical images of 1 mm³ voxel sizes were acquired for each subject using standard T1 sequences (3D MPRAGE sequence, 176 slices). For the co-registration of MR images and MEG data, vitamin E pills were placed during the structural scans at the same position as the coils used for the assessment of head position during MEG recordings.

2.3 | Stimuli

Visual stimuli were created using the Psychophysics Toolbox (Brainard, 1997) version 3 within MATLAB (The MathWorks, Inc., Natick MA). The grating stimuli (circular sine wave gratings; expanding with a speed of 0.3°/s; diameter: 7°; spatial frequency: 3 cycles/°; contrast: 100%) were presented at the right side of the screen on the horizontal meridian at an eccentricity of 5.5° from a fixation spot (diameter: 0.11°) or a cross (diameter: 1.1°, luminance (1140 cd/m²). Background luminance was 145 cd/m².

2.4 | Experimental design

Each subject participated in several sessions distributed over maximally 13 test days. In an introductory session subjects were screened for compliance. They received detailed information about the planned NFB training and the nature of the task. We especially emphasized the importance of participating in the whole sequence of experiments. In the next session, anatomical MRI scans were collected. All subsequent sessions took place in the MEG.

2.4.1 | Pre-training mapping session

The pre-training mapping session served to determine the region from which the feedback signal was to be derived and to select the frequency band of the oscillations whose power was to be converted into the feedback signal. Subjects continuously fixated a fixation cross while a moving grating (see above) was presented every 8 s for 4 s in order to induce gamma oscillations at the retinotopically corresponding site in the visual cortex.

The region from which the feedback signal was derived was identical to the reconstructed source of the stimulus induced gamma oscillations and the frequency band selected for NFB training was 20 Hz wide and centered on the peak frequency of the stimulus induced gamma oscillations. The parameters for this source reconstruction were stored as a spatial filter weight matrix (275 channels × 1,200 sample points) for each subject. A detailed description of signal processing is given below.

2.4.2 | NFB training and task sessions

The NFB training consisted of learning- and task sessions. In both sessions the auditory feedback signal was provided but visual stimuli were presented only in the learning sessions. During these sessions (up to 4)

Nfb training and task

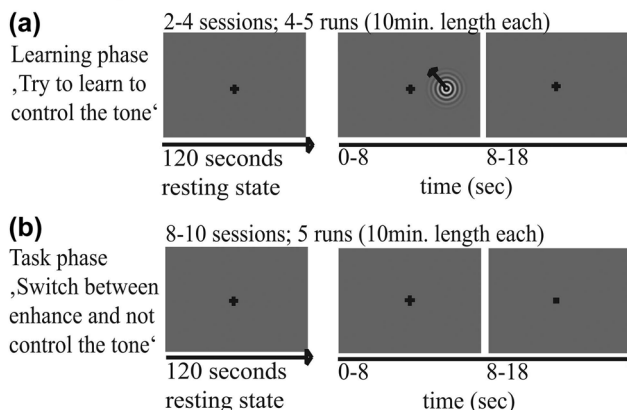


FIGURE 1 Instructions and stimulus sequences for the different phases of the experiment. (a) The learning phase. (b) The switch from the learning to the task phase (c) The task phase. The change of the fixation target indicates the requested task (cross: control the tone, dot: ignore the tone)

subjects could familiarize with the setup and search for strategies to control the feedback signal (pitch of the tone) without pressure to succeed. The subjects were presented with the same grating stimuli as during the mapping session but this time the alternation rate (grating/no-grating) was 8 s. The subjects were asked to “find a strategy to control the pitch of the tone” without further instructions. Once subjects indicated that they had control over the tone the task sessions were initiated (Figure 1).

In the task sessions (8–10 sessions) visual stimuli were absent and subjects had to switch between phases where they should increase the pitch of the tone and phases where they should disregard the pitch fluctuations while fixating the fixation spot to reduce eye movements. The instructions “enhance the pitch” and “ignore the pitch” were indicated by a change of the fixation target (from dot to cross and vice versa) and changed at a rate of 8 s. Each training day (up to $n = 13$) consisted of 4–5 runs. Each run started with a resting state recording (gray screen, fixation cross, 60 s with and 60 s without grating stimulus), followed by the NFB task. Together with the resting state recording each run had a total length of 600 s. The NFB sessions took place at about the same time of the day to avoid diurnal fluctuations and were spread out over maximally 3 weeks. At the beginning of each session, the subjects' head position was calibrated in the MEG helmet to exactly match the position of the respective first session with the aid of a real-time plug-in for head localization developed by FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011) and adapted to our needs. Head positions were determined in 3D coordinates using head localization coils on the nasion and the two ears. During data acquisition, the actual position was continuously updated every 100 ms and deviations from the initial head position were monitored by color changes from green (match) to orange and red (mismatch; Figure 2). Whenever deviations exceeded 5 mm the subject's head position was corrected.

At the end of each training session, the subjects were asked to describe the strategies they used during both, the “enhance” and “ignore” conditions.

Real-time headlocalization

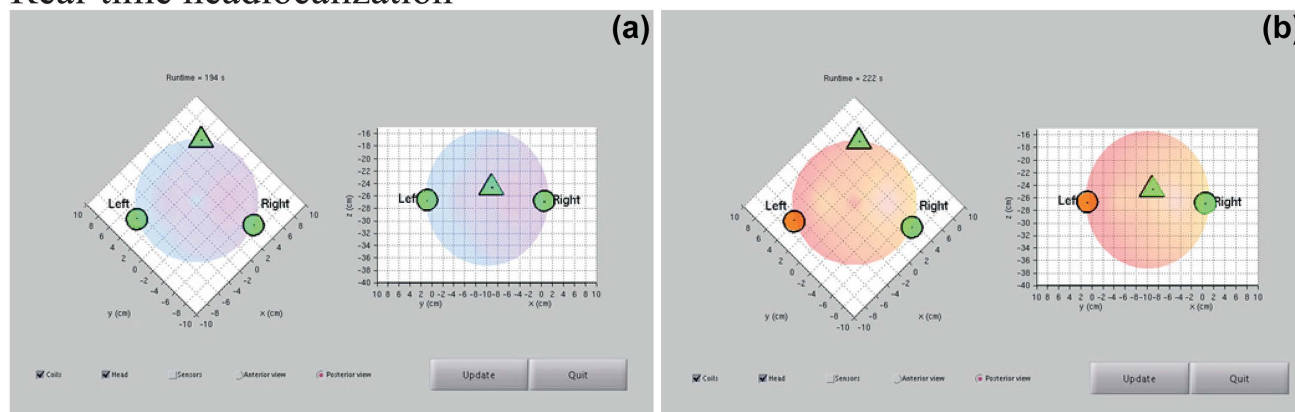


FIGURE 2 Real-time head localization based on the FieldTrip procedure. The real-time head localization visualizes the subjects' head position (right ear, left ear, and nasion) relative to the starting position. On the left all positions match and are therefore green, on the right the head had slightly turned leftwards compared to the original position, which gives an orange spot

2.4.3 | Determination of feedback parameters

Before processing the MEG data we applied visual and automatic artifact detection and rejection routines implemented in the FieldTrip toolbox. Trials with muscle activity were automatically and trials with eye blinks and SQUID sensor jumps visually detected and eliminated.

To identify the frequency of stimulus induced gamma oscillations characteristic for individual subjects we applied a multitaper-based frequency transformation (1–120 Hz) to signals recorded from occipital sensors. The oscillatory component induced by the grating stimulus was extracted by subtracting baseline trials from stimulation trials. For NFB training we converted the power of gamma oscillations within a 20 Hz wide band centered on the peak frequency of the grating induced oscillations into the pitch of a tone signal. To determine the site of origin of this induced activity, that was later used as source of the NFB signal, we applied two methods of source reconstruction: frequency domain beamforming (dynamical imaging of coherent sources [DICS]; Gross et al., 2001) and time domain beamforming (linearly constrained minimum variance [LCMV] (Van Drongelen, Yuchtman, Van Veen, & Van Huffelen, 1996)) as implemented in the FieldTrip toolbox. The frequency domain beamformer was used to localize the sources of oscillatory activity in the selected frequency bands. The time domain beamformer was used to reconstruct the time series at specific locations of interest. Spatial filters were generated for each grid location based on the lead fields and the cross-spectral density matrix for each subject. We used the “common filter” approach by including both, baseline and stimulation data, and calculated the spatial filters required for later on-line processing of the feedback signal. The identified sources were looked up in MNI space using the “wake-forest-university” (WFU) pick atlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). To create a source grid we segmented the individual's MR image and transformed it to a SPM template brain (SPM8 toolbox, <http://www.fil.ion.ucl.ac.uk/sump>). This yielded a transformation matrix for each subject. A regular grid of 1 mm³ was then constructed and warped with the inverse of the individual's transformation matrix. This way we obtained

individual dipole grids for each subject. The lead fields were then calculated for these grid locations with a realistic single shell forward model (Nolte, 2003).

2.4.4 | Real-time data processing pipeline

Because NFB training requires on-line processing a special analysis pipeline had to be developed.

Extraction and processing of the feedback signal

For on-line extraction of the feedback signal a dedicated network connection has been established between the MEG system and an analysis PC. The real-time access to the MEG system was realized using a “buffer”-system developed by the authors of FieldTrip. It is implemented as a multi-threaded application in C/C++ and consists of a network transparent TCP server that allows the acquisition client to stream data sample-wise or in small blocks. The source code was integrated in the MEG acquisition system. This allowed multiple clients to connect and read/write the data events such that an analysis computer could continuously read and process the incoming data.

For the “real-time beamforming” we used the stored pre-calculated spatial filter weights that were extracted from the pre-test mapping data. Segments of data containing 1,200 samples were transferred at intervals of one second. This data matrix (consisting of 275 sensors and 1,200 samples) was then multiplied with the stored, pre-calculated spatial filter weights to constrain the origin of the feedback signal to the source defined during the pre-training mapping session (transposed, 3×275 [x, y, z sensor arrays]). The data were windowed for each (x-, y-, z-) dimension separately using a Hanning window. To extract the power of gamma oscillations in these source data we first performed a Fourier transformation for the frequency range 1–120 Hz and calculated the power (squared absolute amplitude) for the frequencies in the band of interest and its sidebands for each dimension. To maximally “reward” power changes in a narrow band the power of oscillation frequencies below and above the 20 Hz wide band (from 30

to 120 Hz) selected for training was weighted with a sigmoid function and subtracted from the power of the band selected for NFB before conversion in pitch changes of the feedback tone (Equation 1).

$$\text{sig}(t) = \frac{1}{1+e^{-t}} = \frac{e^t}{1+e^t} = \frac{1}{2(1+\tan(\frac{t}{2}))} \quad (1)$$

This procedure resulted in an output value that reflected the weighted, narrow-band gamma-band power at the selected location in source space. The respective amplitude value was then linearly mapped onto tone frequencies ranging from 100 to 400 Hz and updated every second. To ensure smooth tone transitions and to avoid inducing evoked responses, a linear smoothing function was applied with a transition time of 400 ms.

2.5 | Off-line data analysis

All off-line analyses were performed with MATLAB and the open source MATLAB toolbox FieldTrip, Version 2012 01-05. In order to identify the source of the self-generated gamma oscillations and their frequency spectrum we applied beamforming methods and two types of frequency transformation. To investigate task-related effects at the training location we analyzed the cleaned MEG data recorded during the NFB task ("ignore the tone" + "control the tone" = 16 s). LCMV beamforming and the common filter approach were applied to construct 'virtual channels' for the training location of each subject. For the time frequency transformation we applied multitaper-based time frequency transformation for the frequency range 1–120 Hz. For baseline correction of the task related signals we used the baseline segment starting 4 s after the end of the respective last task (4–8 s) to avoid leakage of task related activity. To assess task related effects ("control the tone" – "ignore the tone") we compared the respective power distributions in the two task intervals (8–12 s and 12–16 s) using time resolved statistics (dependent *t* test, multiple comparison correction, alpha = 0.05, number of randomization = 1,000, cluster-alpha = 0.001) and tested the two task intervals separately against the baseline. To analyze the frequency spectrum we used the multitaper method based on discrete prolate spheroidal sequences (Slepian sequences; 10 Hz smoothing, dpss multitaper, window width = 0.5 s). To analyze the frequency spectrum in a time resolved way we used the multitaper method based on Slepian sequences with a sliding window approach (50 ms steps, 5 Hz smoothing, dpss multitaper, window width = 0.5 s).

To determine the frequency specificity of NFB effects we further analyzed the significance of spectral changes of signals derived from the trained location. We separately assessed task-related changes for the complete gamma-band (30–120 Hz), the band of training, and the sidebands, respectively. As sidebands we defined the frequency ranges from 30 Hz to the lower boundary of the band selected for training and from the upper boundary to 120 Hz. NFB training was considered as frequency specific if subjects showed higher task-related power increases in the band of training than in the sidebands.

To assess the site specificity of NFB training we reexamined the location of the source of task related gamma oscillations. To this end we split the task period into two 4-s segments (0–4 and 4–8 s) and

performed DICS beamforming. For the time frequency transformation we considered the spectrum from 1 to 120 Hz and determined the power within the band of training for each voxel in source space. Source level statistics were calculated using *t* tests (cluster-based multiple comparison, correction for "false discovery rate" (FDR, Benjamini & Hochberg, 1995), alpha = 0.05, number of randomization = 1000, cluster-alpha = 0.001). We then identified local cluster maxima for statistically significant voxels by scanning all voxels for maximal values in a 26 voxel neighborhood. These clusters were then related to MNI coordinates and located according to the MNI Structural Atlas and the Juelich Histological Atlas (Desikan et al., 2006). To assess the site specificity of the training effects we then calculated the Euclidian distance (*d*) between the region selected for training (A [MNI_x, MNI_y, MNI_z]) and the location of the clusters showing specific training effects (B [MNI_x, MNI_y, MNI_z]) as specified in Equation 2.

$$d = \sqrt{(A(\text{MNI}_x) - B(\text{MNI}_x))^2 + (A(\text{MNI}_y) - B(\text{MNI}_y))^2 + (A(\text{MNI}_z) - B(\text{MNI}_z))^2}$$

2.5.1 | Analysis of the feedback signal

As the pitch of the feedback signal is supposed to reflect the frequency specific power changes of the oscillatory activity generated in the selected target region, we calculated descriptive statistics (mean, variance) of the tone signal and compared baseline and task periods using the two sided *t* test for equal means and the two-sample *F* test for equal variances. Multiple comparisons can induce type I errors (incorrect rejection of a true null hypothesis). Therefore we corrected the *p* values for "false discovery rate" as described in (Benjamini & Hochberg, 1995).

2.5.2 | Training-related mechanisms

To identify activity patterns other than those targeted by NFB training but associated with the various outcomes of the training we performed a whole brain analysis of changes of oscillatory activity in sensor space for the frequency range below the trained bands (1–30 Hz) and computed averages for three groups of subjects: (a) all subjects, (b) subjects that succeeded, and (c) subjects that failed to perform the task. This time we used only one taper (Hanning taper), which is common for the analysis of lower frequency bands and averaged the data for each subject group for central, frontal and temporal sensors. We used DICS beamforming to obtain the sources of theta-band (frequency 5 ± 2 Hz, task = 0–1 s, baseline = –1–0 s), alpha-band (frequency 12 ± 3 Hz, task time = 2–4 s, baseline time = –4–2 s) and beta-band activity changes (frequency 18 ± 3 Hz, task time = 2–4 s, baseline time = –4–2 s). The MNI coordinates and cortical areas of the respective sources were identified using the MNI atlas and WFU toolbox.

3 | RESULTS

3.1 | Training parameter

Table 1 summarizes the parameters used for NFB training (frequency band and cortical site) that were determined during the first session and differed for each of the ten subjects.

TABLE 1 Participants age, gender and training parameters

Sub	Gender	Age	Band of training (Hz)	Peak frequency (Hz)	Region of training MNI (x, y, z) voxel index	
1	w	24	55–75	65	[−10 −90 0]	2,915
2	w	24	35–55	45	[−10 −80 10]	3,285
3	m	21	45–65	55	[−10 −90 −20]	3,629
4	m	26	45–65	55	[−10 −90 20]	3,629
5	m	22	52–72	62	[−40 −90 10]	2,947
6	w	21	38–58	48	[−10 −100 0]	2,898
7	w	22	52–72	62	[−10 −80 30]	4,003
8	w	20	55–75	65	[0 −90 0]	3,270
9	m	32	32–52	42	[−20 −90 20]	3,628
10	m	19	65–85	75	[−40 −90 10]	3,269

The region from which the feedback signal was derived is indicated by MNI coordinates (x, y, and z) and voxel-indices. The band of training is 20 Hz wide and centered on the peak frequency of gamma oscillations evoked by a grating.

3.2 | Muscle activity

When analyzing the frequency spectrum of task dependent changes in the power of oscillatory activity, we found that 2 of 10 subjects probably increased muscle activity in a task-related way. In these subjects (sub1, sub7) we observed spectral patterns that tend to be associated with the contraction of temporalis and masseter muscles rather than neuronal activity (Donnell, Berkhout, & Adey, 1974; Goncharova, McFarland, Vaughan, & Wolpaw, 2003; Whitham et al., 2007). We therefore suspected that two subjects used muscle rather than neuronal activity to control the feedback signal. This is a notorious problem in NFB studies as pointed out by Thibault, Lifshitz, Birbaumer, and Raz (2015). To stay on the safe side we excluded these two subjects from further analysis.

3.3 | Task-related changes of gamma power at the location of training

Although task-related changes of oscillation power occurred over the entire frequency spectrum (1–120 Hz, see time frequency plots) we performed quantitative analyses only for the power changes in the gamma-band (>30 Hz). Task-related changes in the gamma-band occurred in 7 of 8 subjects (all but sub 4). Significance testing for those 7 subjects revealed that these changes were significant within the band of training in 5 of 7 subjects (sub 2, sub 3, sub 5, sub 8, and sub 9). Figure 3 shows the task-related spectral changes at the respective training locations for the 5 successful subjects (A) and the results of the statistical testing (B).

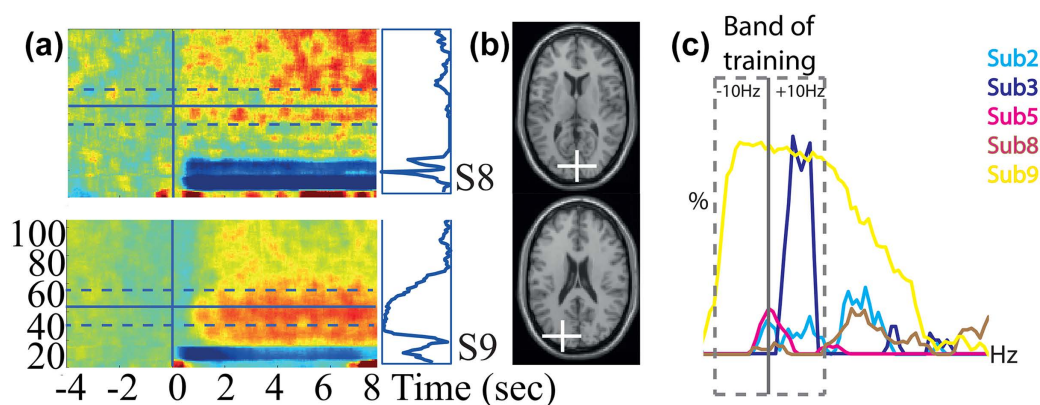


FIGURE 3 (a) Task-related spectral changes at the location of training (virtual channel) for two successful example subjects. The vertical bars indicate task onset (control the tone). The horizontal bars indicate the individual's band of training, (b) Location of sources used for training on the individuals' MRI scans. (c) Task related power changes (relative change, task vs. baseline), centered around the individuals band of training. Significant time bins within the gamma-band are counted and added up

TABLE 2 Location of sources showing significant training related increases of gamma power in the trained band

Sub	ROT (MNI)	Hotspot MNI coordinates and distance to ROT in cm (sorted by significance)				
		1	2	3	4	5
2	[-10 -80 10]	[20 -80 -20] 4.24 cm	[-20 -80 -20] 3.16 cm	[-20 -70 -20] 3.32 cm	-	-
3	[-10 -90 20]	[20 -90 0] 3.6 cm	[30 -80 -20] 5.7 cm	-	-	-
5	[-30 -70 0]	[-40 -90 10] 1 cm	-	-	-	-
8	[0 -90 10]	[20 -90 -20] 3.61 cm	[-30 -80 -10] 3.74 cm	[-50 -80 30] 5.48 cm	[10 -70 -10] 3 cm	[-30 -100 0] 3.32 cm
9	[-20 -90 20]	[-30 -90 30] 1.41 cm	-	-	-	-

The hotspot MNI coordinates are used to calculate the distance to the region of training.

3.4 | The bandwidth of gamma-band changes at the trained site

Due to the preprocessing of the feedback signal (see Section 2) subjects were encouraged to enhance gamma power within a 20 Hz wide band centered on the frequency of the stimulus induced gamma oscillations. To examine whether subjects were able to restrict power changes to the trained frequency band we compared the power changes in the trained band to those in the sidebands. This is a conservative measure as we considered as "side bands" a frequency range of 70 Hz which is much wider than the 20 Hz of the band of training. The lower and higher cut-off frequencies for the determination of the side bands were 30 and 120 Hz, respectively. Thus, side band power was computed from a 70-Hz wide band (90–20 Hz for the training band). Of the 5 subjects exhibiting significant increases in gamma-band power in the band of training, 4 showed stronger increases in the band of training than in the side bands. The respective differences were: + 4.15% (sub 9), + 3.75% (sub 2) + 2.5% (sub 8), + 1.94% (sub 6) and + 0.38% (sub 3). Only subject 5 increased the power more in the sidebands than in the band of training. Interestingly in sub 5 the increase in gamma-band power was accompanied by a strong task related increase in the beta band.

3.5 | The spatial specificity of gamma-band power changes

To examine the spatial specificity of task-related increases in the gamma-band we reconstructed the sources of the task-related gamma-band activity and determined the distance to the site selected for training as the Euclidian distance (d) between the region of training (A) and each of the identified local maxima (hotspots B). For all successful (5 of 5) subjects the sources of significant task-related activation in the trained band were located in the visual cortex. The exact locations in MNI space are specified in Table 2. Sub 2 had two hotspots that were located in the left and right occipital lobes. For the trained hemisphere the distance between the hotspot and the site selected for training was 3.16 cm. For sub 3 hotspots were found in right V1 (BA17) and V2 (BA18), the distances to the site selected for training were 3.6 and 5.7 cm, respectively. For sub 5 the hotspot was located in left V3, 1 cm away from the trained site. Sub 8 had hot spots in left V1 (BA17) and V2 (BA18), in V3 bilaterally and in left V4. For the trained left hemisphere the distances between the hotspot and the site selected for training were 3.74, 5.48, and 3.32 cm, respectively. Sub 9 had a hotspot in left V1 (BA17)/V2 (BA18) which was located 1.41 cm from the site selected for training. The average distances of all hotspots ipsilateral to the designated training site was 2.77 cm (range: 1–5.48 cm). The best match between training site and the source of enhanced gamma power was found for sub 5 and sub 9, with $d = 1$ and 1.41 cm, respectively.

3.6 | Modifications of the feedback signal

As the feedback signal reflects the dynamic changes of gamma power at the site and in the frequency band selected for training, we expected additional information on the training process by

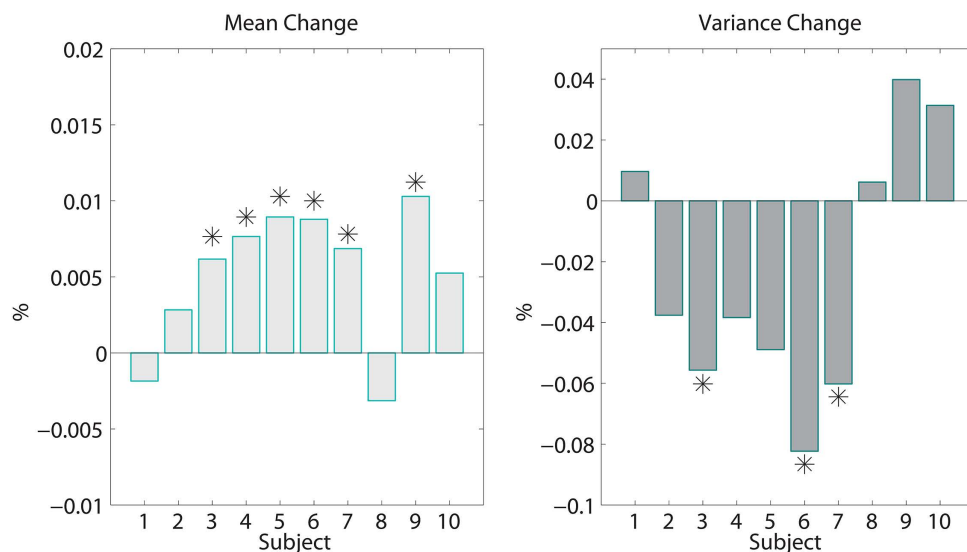


FIGURE 4 Task-related changes in the mean and variance of the feedback tone for each subject separately. Significant differences in the mean and the variance between task and baseline were calculated with *t* tests and *F* test, respectively. Significance is indicated by stars ($p < .05$)

characterizing the changes of the feedback signal. In all subjects the pitch changes of the feedback tone showed task-related changes in the mean and/or variance (Figure 4 and Table 3).

In 8 of 10 subjects (all but sub 1 and sub 8) the average tone frequency was enhanced during the task phase (compared to the baseline phase); in 6 of 8 these changes were significant in the two-sided *t* test (sub 3, sub 4, sub 5, sub 6, sub 7, and sub 9). In 2 subjects (sub 1 and sub 8) there was a paradoxical decrease of mean tone frequency but this decrease was not significant.

In 6 of 10 subjects (sub 2, sub 3, sub 4, sub 5, sub 6, sub 7, and sub 8) the variance of the pitch changes decreased during the task phase; in 3 of 6 (sub 3, sub 6, and sub 7) these decreases were significant (*F* test for unequal variance). The task-related increases in variance in 4 of 10 subjects were not significant. The changes in mean and

variance were anticorrelated, task-related increases in the mean co-occurred with task-related decreases in the variance and vice versa. We found this pattern in 7 of 10 (all but sub 1, sub 9 and sub 10). Interestingly, all subjects that significantly decreased the variance of the tone (and therefore achieved a more sustained control of the tone) also significantly increased the mean of the tone.

These results agree with the trend revealed by the analysis of the neuronal signal. Only two subjects gave inconsistent results. Sub 1 and sub 8 slightly decreased the mean of the feedback tone during the task, even though it increased neuronal activity within the gamma-band. A potential explanation could be that those subjects only increased gamma-band power during very short periods but also showed strong decreases of power in between such that the overall mean might be slightly decreased even though there were episodes

TABLE 3 Mean and standard deviation of the pitch changes during task and baseline conditions

Sub	Task (mean, SD)	Baseline (mean, SD)	<i>T</i> (<i>p</i> value, FDR corrected)	<i>F</i> (<i>p</i> value, FDR corrected)
1	255.6967 (40.9628)	256.1714 (40.7670)	<i>T</i> = 0.5809 (<i>p</i> = .5613)	<i>F</i> = 1.0096 (<i>p</i> = .7891)
2	256.3434 (40.4889)	255.6194 (41.2720)	<i>T</i> = 1.0906 (<i>p</i> = .3061)	<i>F</i> = 0.9624 (<i>p</i> = .1361)
3	251.6807 (39.8775)	250.1375 (41.0362)	<i>T</i> = 2.3490 (<i>p</i> = .0314)	<i>F</i> = 0.9443 (<i>p</i> = .0421)
4	245.0954 (38.3083)	243.2341 (39.0650)	<i>T</i> = 2.9632 (<i>p</i> = .0076)	<i>F</i> = 0.9616 (<i>p</i> = .1361)
5	250.3277 (38.6007)	248.1104 (39.5810)	<i>T</i> = 3.4933 (<i>p</i> = .0021)	<i>F</i> = 0.9511 (<i>p</i> = .0724)
6	246.3936 (37.7850)	244.2481 (39.4431)	<i>T</i> = 3.4209 (<i>p</i> = .0021)	<i>F</i> = 0.9177 (<i>p</i> = .0018)
7	263.8448 (45.5010)	262.0469 (46.9356)	<i>T</i> = 2.3954 (<i>p</i> = .0314)	<i>F</i> = 0.9398 (<i>p</i> = .0343)
8	253.7876 (41.2620)	254.5876 (41.1356)	<i>T</i> = -1.1960 (<i>p</i> = .2896)	<i>F</i> = 1.0062 (<i>p</i> = .7891)
9	245.6777 (38.4122)	243.1757 (37.6688)	<i>T</i> = 4.0519 (<i>p</i> = .0005)	<i>F</i> = 1.0399 (<i>p</i> = .1361)
10	247.5003 (40.7577)	246.2080 (40.1331)	<i>T</i> = 1.9684 (<i>p</i> = .0701)	<i>F</i> = 1.0314 (<i>p</i> = .2231)

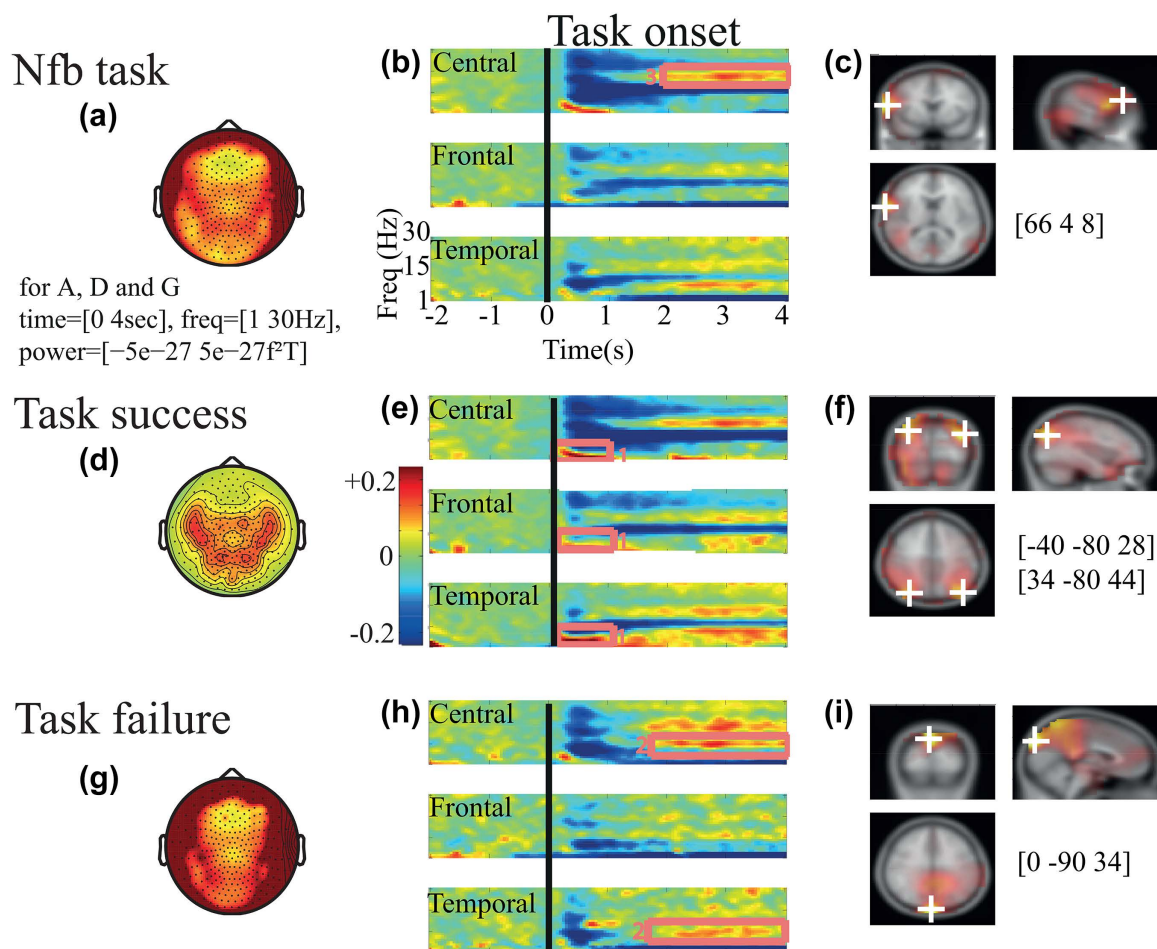


FIGURE 5 Task associated changes in lower frequency bands in other brain regions. Averages across all subjects (a–c), across successful subjects (d and e) and across subjects that failed to increase gamma-band power (g–i). The images on the right (c, f, and i) show the results of the source localization procedure (no masking)

with high gamma-power. This interpretation is supported by the fact that the variance of the feedback tone was enhanced in those subjects.

3.7 | Task dependent changes in lower frequency bands

To identify activity patterns other than those targeted by NFB training but associated with the training and its various outcomes, we performed a whole brain analysis of changes of oscillatory activity in sensor space for the frequency range below the trained bands (1–30 Hz) and computed averages for 3 groups of subjects: (a) all subjects (Figure 5a–c), (b) subjects that succeeded (Figure 5d–f), and (c) subjects that failed to perform the task (Figure 5g–i). We analyzed activity generated during the task and the baseline phase (task: 16 s “control” and baseline: “ignore” the tone). In the grand average across all subjects we found increased beta-band activity (peak 18 Hz, range: 16–20 Hz) and source analysis (see Section 2) revealed that it originated from right precentral/frontal and parietal regions (MNI [66, 4, 8]). In addition there was an increase of power in the theta range (peak 5 Hz, range: 3–7 Hz) over central regions. When considering only the 5 successful subjects the increase in theta-band power (peak 5 Hz, range: 3–7 Hz) became

even more pronounced and now also for sources in central/frontal and temporal regions bilaterally (MNI [–40, –80, 28], [34, –80, 44]). In addition there was a marked suppression of alpha oscillations. When averaging only across unsuccessful subjects we found (additionally to the increased beta-power, that was also present in the other groups) increased alpha-band power (peak 10 Hz, range: 8–12 Hz) with sources in primary visual cortex ([0, –90, 34]).

3.8 | Strategies of the successful subjects

We analyzed the descriptions of the subject’s strategies for each of the successful subjects. Table 4 summarizes the results of this analysis.

We found that 3 of 5 subjects (sub 2, sub 8, and sub 9) used imagery related strategies to increase the feedback signal. During the NFB task they alternated between states where they imagined visual situations, contrast rich images and their rotation, complex scenes, persons or objects during the “control the tone” phase and states of idling during the “ignore the tone phase”. Sub 9, the most successful performer, reported that he/she imagined concrete situations, like sport exercises or imagined portraits or faces and changed their size, to perpetuate the image. 2 of 5 subjects (sub 3 and sub 6) used attention

TABLE 4 Strategies of the successful subjects

Sub	Task	Baseline
2	Imagination of positive, nice situations Focusing on funny thoughts Increasing positive feelings Increasing mood by positive thoughts	Think of nothing Let go
3	Focusing on a point Focusing on the screen Focusing on breathing Focusing attention Visualizing objects/ persons/ situations/ places	Let go Let thoughts pass by Not focusing on tone or on trying to control the tone Relaxing
8	Speedily alternation of thoughts Focusing on emotions related to extreme situations (for example imagine scenes from car accidents)	Thinking of nothing Focusing on internal state Focusing only on one thought Focusing on relaxing conditions (for example low heartbeat)
9	Imagining concrete situations Mentally rotating objects Thinking of simple, always new, contrast rich images with clear contours (black and white) Imagining sport exercises Imagining portraits/ faces and change their size	Thinking of nothing

related strategies. These subjects described attentional shifts between task and idling phases. They alternated between focusing on the screen and paying no attention.

Interestingly two subjects (sub 2 and sub 8) reported that emotions had a beneficial effect on their ability to enhance the pitch. These emotions could be either positive because associated with happy situations (sub 2) or negative because associated with stressful events (sub 8).

During the “ignore” condition all subjects used strategies of not attending. They described for example to “let go attentional focus” or to “think of nothing.”

4 | DISCUSSION

The present results indicate that human subjects can intentionally modulate the power of gamma oscillations in lower areas of the visual cortex when they receive auditory feedback about the current amplitude of gamma oscillations. In some subjects this modulation was restricted to the narrow frequency band from which the feedback signal was derived and to the cortical region from which the feedback signal was recorded. In the grand average across all subjects we found that the attempts to modulate the feedback signal were associated with enhanced beta oscillations in fronto-parietal areas. In the averages across subjects capable of controlling their gamma oscillations there was an additional increase of theta oscillations over central, frontal and temporal regions.

4.1 | Methodological considerations

Our findings confirm that MEG data can be used to extract signals from well-defined neuronal sources sufficiently fast to use them for NFB training. This is in line with other research (Boe et al., 2014; Florin, Bock, & Baillet, 2014; Ora et al., 2013; Sudre et al., 2011) and suggests that methodological limitations of NFB protocols addressed by Thibault

et al. (2015) such as the spatial smearing of EEG signals and the bad spatial resolution of EEG recordings might be overcome with source-level based NFB approaches and MEG recordings.

In contrast to most previous studies (Boe et al., 2014; Florin et al., 2014; Ora et al., 2013; Sudre et al., 2011) we defined the cortical site for the extraction of the feedback signal not according to anatomical but to functional criteria. In addition we individually adapted the oscillation frequency used for NFB training to the subjects' stimulus induced gamma frequency in order to account for the inter-individual frequency variability of gamma oscillations (Hoogenboom et al., 2006; Schwarzkopf et al., 2012). This approach precludes compilation of population averages but has the great advantage to allow assessment of the specificity of NFB effects both with respect to anatomical location and oscillation frequency.

Even though we had used a combination of methods (MEG, source reconstruction, subtraction of side bands) that are optimized to reduce far field effects caused by volume conduction and contamination by broadband muscle activity, two subjects have apparently succeeded to effectively control the feedback signal by differential activation of occipital and temporal muscles. We inferred this from the characteristic broadband frequency spectrum of the self-generated activity. This should be taken as a warning for colleagues designing NFB protocols, especially if signals are extracted from EEG recordings that are much more susceptible than MEG recordings to artifacts caused by volume conduction and muscle activity. A detailed, simulation based analysis of these muscle artifacts is the topic of a methods paper (in prep).

4.2 | Mechanisms

The fact that subjects were able to modulate self-generated rather than only stimulus induced gamma oscillations within a narrow frequency band and a circumscribed region in the visual cortex underlines the efficiency and selectivity with which top-down projections can

modulate the state of early sensory processing stages. Gamma oscillations result from network interactions between fast spiking parvalbumin containing (PV+ basket cells) and/or somatostatin containing (Som+) GABAergic interneurons that are in turn reciprocally coupled with pyramidal cells (the PING circuit, (Whittington, Traub, Kopell, Ermentrout, & Buhl, 2000; Veit, Hakim, Jägle, Sejnowski, & Adesnik, 2017). Gamma oscillations are evoked when this recurrent circuit is sufficiently activated either physiologically, e.g. in sensory cortices by external stimuli via thalamo-cortical afferents (C. Gray & Singer, 1989), or artificially with pharmacological (Cunningham, Davies, Buhl, Kopell, & Whittington, 2003) or optogenetic methods (Cardin et al., 2009). The frequency of these oscillations increases with the excitatory drive (Ray & Maunsell, 2010, Klein et al., personal communication), stimulus speed (Gray, Engel, König, & Singer, 1990) and the complexity of stimuli (Lima, Singer, & Neuenschwander, 2011). The mere fact that gamma oscillations occur also without sensory stimulation is per se not surprising as they are often observed in conjunction with self-generated activity: In motor areas in relation with intentional acts and the preparation of movement (Fetz et al. 1973, Engelhard et al., 2013, Schoffelen, Poort, Oostenveld, & Fries, 2011), in cortical areas involved with higher cognitive functions they occur during retrieval from long (Kaiser et al., 2003; Roux & Uhlhaas, 2014) as well as short term memory (Lundqvist et al., 2016), they are observed in conjunction with the slow delta oscillations reflecting shifts between down- and up-states (Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008) and in the hippocampus they occur together with theta oscillations (Buzsáki, 2002; Lisman & Jensen, 2013). It is generally held that the main driving force of early sensory areas is provided by sensory signals and that top-down projections have only a modulating effect on sensory evoked responses, whereby these effects are generally weak in early sensory cortices (Fries, Reynolds, Rorie, & Desimone, 2001b). Thus, it is quite remarkable that subjects were able to intentionally enhance gamma oscillations in early visual areas. One possibility is that certain top down cortico-cortical connections actually have driving functions as suggested by recent anatomical data (Markov & Kennedy, 2013). This interpretation would also agree with the evidence from fMRI experiments showing activation of low level visual areas during imagery (see below) and with recent concepts on predictive coding (Bauer et al., 2014). Another, non-exclusive possibility is that the drive necessary to induce oscillations was mediated by cortico-thalamo-cortical loops. Our data do not allow us to distinguish between these possibilities.

The high topological specificity of the gamma enhancement suggests that the gamma inducing activity was mediated by circuits involved in controlling selective attention, because the effects of attention show similar topological selectivity. Expectancy and attention enhance the amplitude of gamma oscillations induced by the selected stimuli (Bauer et al., 2014; Fries, et al., 2001b; Landau, Schreyer, Van Pelt, & Fries, 2015; Lima et al., 2011; Tallon-Baudry, Bertrand, Hénaff, Isnard, & Fischer, 2005) and electrophysiological studies on the spatial and feature selectivity of attention mechanisms have revealed a degree of selectivity that largely suffices to explain the present data (Bosman et al., 2012; Gregoriou et al., 2012; Keil & Müller, 2010; Motter, 1993; Steinmetz et al., 2000; Verghese, Kim, & Wade, 2012). But there is yet

no evidence that focusing attention in the absence of sensory input is alone sufficient to induce gamma oscillations in early sensory areas. As attentional mechanisms can be trained (Lutz, Slagter, Dunne, & Davidson, 2008; van Leeuwen, Singer, & Melloni, 2012) subjects may have learned to engage the attention networks sufficiently to activate the oscillatory circuits in the absence of sensory stimuli. Such engagement is supported by the finding that the NFB training was associated with enhanced beta oscillations over fronto-parietal regions. Other NFB studies have also shown engagement of fronto-parietal and cingulo-opercular networks (Ninaus et al., 2013) and at least the fronto-parietal areas are part of the attention network (Miller & Buschman, 2013). They have been shown to engage in coherent beta oscillations during attention tasks (Buschman & Miller, 2010) and beta oscillations are a hallmark of top-down modulation (Bastos et al., 2015). However, additional factors must have played a role because the beta network was activated also in subjects who failed to reach our, admittedly strict, criteria for the success of the NFB training.

Another and non-exclusive possibility is that subjects applied strategies of imagery to increase gamma oscillations in early visual cortex. The visual cortex has been suggested to provide memory templates for working memory and visual imagery (Albers et al., 2013) and to serve as a “dynamic blackboard” (Albers et al., 2013; Tong, 2003), a “multi-scale cognitive blackboard” (Roelfsema and de Lange, 2016) or a “high-resolution buffer system” (Lee et al., 2005). Visual imagery is associated with enhanced BOLD signals in early visual cortex (Goebel, Khorram-Sefat, Muckli, Hacker, & Singer, 1998; Kosslyn, Behrmann, & Jeanerod, 1995; Slotnick, Thompson, & Kosslyn, 2005 but see Kaas, Weigelt, Roebroeck, Kohler, & Muckli, 2010) and this activation could reflect the read out of information stored in the functional architecture of visual cortex, especially if low level features are to be imagined (Pearson, Naselaris, Holmes, & Kosslyn, 2015). Increased BOLD activity is a reflection of enhanced neuronal activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001) and correlates particularly well with the power of gamma oscillations (Niessing et al., 2005). Because read out of engrams has been shown to be associated with enhanced gamma oscillations (see Section 1) there is an interesting convergence between the finding that imagery enhances BOLD signals in early visual cortex and the reports of our subjects who had used imagery to enhance gamma oscillations. The hypothesis that imagery could have been a strategy to enhance gamma oscillations is further supported by the finding that only the successful subjects exhibited prominent theta activity over frontal, central and temporal regions while attempting to enhance gamma oscillations in the visual cortex. Theta oscillations have been shown in numerous studies to be associated with the encoding and read out of memories in diverse brain areas (Başar, Başar-Eroglu, Karakaş, & Schuermann, 2001; Buzsáki & Moser, 2013; Klimesch, Freunberger, & Sauseng, 2010; Osipova et al., 2006; Roux & Uhlhaas, 2014)—albeit to the best of our knowledge not in the visual cortex. Thus, the theta-band power increase might reflect activation of memory templates. Theta-gamma cross-frequency coupling is well established (Canolty et al., 2006) and has been discussed in the context of numerous functions, such as modulation of reaction times (VanRullen et al., 2011), memory encoding, spatial navigation (Buzsáki & Moser,

2013) and multiplexing of working memory contents (Lisman and Jensen, 2013).

Imagery could also account for the variable size and location of the sources of NFB related gamma enhancement. If subjects imagined well localized structured visual objects in a particular area of the visual field, one expects foci of activity to be more circumscribed and located in lower visual areas than if subjects just imagined complex scenes. As the debriefing results suggest, this has apparently been the case. Our most successful subject (sub 9) reported to imagine precise objects during the task.

4.3 | Frequency specificity

We considered as successful only those subjects who had managed to enhance gamma power significantly more in the narrow band that was selected for the control of the feedback tone than in the adjacent parts of the spectrum. This criterion may have been too strict as the flanking spectrum comprised a broad range of both lower and higher frequencies. Some subjects ($n = 2$, those suspected to use muscle activity are not considered) successfully enhanced gamma oscillations in the selected band but in addition also increased the power of higher frequencies. This raises the question whether subjects were actually capable of controlling the frequency of the self-generated gamma oscillations. One possibility is that this was not the case and that the preferential increase within the selected band resulted solely from the fact that this band was centered deliberately on the peak frequency of the gamma oscillations evoked by visual stimulation and thus corresponded to the subjects' "preferred" gamma band. As mentioned above the frequencies of induced gamma-band responses show high inter-individual variability but are characteristic like finger prints for individuals (Hoogenboom et al., 2006). We had chosen the respective preferred bands for training to facilitate the task because we had doubts whether subjects would at all be capable of inducing self-generated gamma oscillations in early sensory cortices. Still, since the frequency of gamma-band oscillations depends within a limited range on the drive impinging on the oscillatory circuits, subjects should have had the option to influence the frequency of the oscillations by modulating the intensity of the top-down signal. Comparing the spectra of the stimulus induced oscillations with those during the task in the "successful" subjects does suggest that they were actually able to control not only the amplitude of oscillations in the preselected band but also the frequency of the oscillations. However, since we did not perform control experiments by training non-preferred bands, we cannot draw any firm conclusions.

4.4 | Signatures of failure

Some subjects ($n = 3$) failed altogether to enhance gamma power in the selected voxel and frequency band. The debriefing suggested that these subjects had found no viable strategy to control the tone. To avoid any experimenter induced bias we refrained from suggesting strategies that we thought might work such as covertly focusing attention or imagery. The spectrograms of those who failed to accomplish

the task showed a marked increase of oscillations around 12 Hz, typically referred to as alpha oscillations (Berger, 1929; Jensen & Mazaheri, 2010). Gamma- and alpha-band activity are usually anti-correlated (Bastos et al., 2015; Händel, Haarmeier, & Jensen, 2011; Jensen, Bonnefond, Marshall, & Tiesinga, 2015; Jensen, Gips, Bergmann, & Bonnefond, 2014; Klimesch, 2012). Most authors interpret alpha-band power increases as reflection of inhibitory processes (Händel et al., 2011, for a review see Jensen et al., 2014). However, since alpha oscillations can become synchronized over large cortical distances—probably via thalamic pacemakers (Saalmann, Pinsk, Wang, Li, & Kastner, 2012; Saalmann & Kastner, 2011)—they have also been assigned a role in synchronizing oscillations in higher frequencies over larger distances by virtue of cross frequency coupling (Canolty & Knight, 2009; Fitzgerald, Valentin, Selway, & Richardson, 2013). Our data do not allow us to distinguish whether the increased alpha activity in our unsuccessful subjects was the consequence of their inability to enhance gamma power and simply reflects a default state or whether it had a causal role as an inhibitory process that prevented the subjects of raising excitability of the visual cortex.

4.5 | Applications of gamma NFB

This study provides evidence that gamma oscillations can be upregulated intentionally with considerable topological specificity even in early sensory areas, if a well-controlled recording and feedback regime is applied. As top-down effects are generally weak in low level sensory cortices (Goebel et al., 1998), this suggests that gamma oscillations should be controllable also in other brain regions and probably more reliably. Over the last decade a large number of studies have established close correlations between abnormalities of gamma oscillations and their synchronization across cortical areas on the one hand and psychiatric conditions such as schizophrenia, autism spectrum disorder and Alzheimer's disease on the other (Phillips & Silverstein, 2003; Spencer et al., 2004, 2009, Uhlhaas & Singer, 2006, 2010). Unfortunately these correlations do not allow one to infer causal relations. It is thus unclear whether the abnormal dynamics are simply reflections of disturbed temporal coordination, the latter being an epiphenomenon of other pathologies or whether the reduced temporal coherence among distributed processors is actually the cause of the cognitive impairments associated with these disease states. In case the latter is the case it might be possible to improve the clinical conditions by NFB regimes that enhance gamma oscillations in selected brain regions. One might even consider to not only train for the enhancement of oscillation power but to also train for enhanced coherence across regions, as this is the most abnormal variable in disease states (Uhlhaas et al., 2006; Uhlhaas & Singer, 2010). However, this requires further and quite challenging developments of methods for the real-time extraction of coherence measures. Finally, a strong incentive for NFB enhanced gamma activity may come from the recent discovery of a totally unexpected inverted causal relation between gamma oscillations and the development of Alzheimer's disease (Iaccarino et al., 2016). This study showed in a transgenic mouse model of hereditary Alzheimer that entrainment of neuronal ensembles in gamma oscillations at 40 Hz

reduced the synthesis of A β , the substrate for plaques, and accelerated its degradation by activation of microglia. The abnormal gamma oscillations found in Alzheimer's patients could thus be a facilitating factor in the development of the disease rather than a consequence of the degenerative processes. The authors showed that the well-established entrainment of gamma oscillations in the visual system by flicker light stimulation (Rager & Singer, 1998) had the same effect as optogenetically induced gamma. Because entrainment of gamma oscillations with sensory stimuli is restricted to early stages of sensory cortices that are affected only at late stages of the disease, NFB methods might be the appropriate tool for the non-invasive entrainment of gamma oscillations in brain structures remote from sensory input. However, as the results of this study suggest, approaches to modify high frequency oscillations will require quite advanced techniques, ideally based on MEG recordings, to extract feedback signals from the desired brain region and to avoid training muscle activity.

CONFLICT OF INTEREST DECLARATION

We have no conflict of interest to declare. We have no competing interest to declare. All authors have seen and approved the manuscript being submitted. This work is the author's original work. On behalf of all Co-Authors, the corresponding Author has full responsibility for the submission. The research has not been published elsewhere. All listed authors have contributed significantly to this work. The ethical committee of the University of Frankfurt did consent to this work.

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