Categorized EEG Neurofeedback Performance Unveils Simultaneous fMRI Deep Brain Activation

Sivan Kinreich[1,3], Ilana Podlipsky[3], Nathan Intrator[4], and Talma Hendler[1,2,3]

[1] Department of Psychology, Tel Aviv University, Tel Aviv, Israel
[2] Department of Physiology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3] Functional Brain Center, Wohl Institute for Advanced Imaging, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israe
[4] School of Computer Science , Tel Aviv University, Tel Aviv, Israel

Abstract. Decades of Electroencephalogram-NeuroFeedback (EEG-NF) practice have proven that people can be effectively trained to selectively regulate their brain activity, thus potentially improving performance. A common protocol of EEG-NF training aims to guide people via a closed-loop operation shifting from high-amplitude of alpha (8-14Hz) to high-amplitude of theta (4-7 Hz) oscillations resulting in greater theta/alpha ratio (T/A). The induction of such a shift in EEG oscillations has been shown to be useful in reaching a state of relaxation in psychiatric conditions of anxiety and mood disorders. However, the clinical implication of this practice remains elusive and is considered to have relatively low therapeutic yield, possibly due to its poor specificity to a unique brain mechanism. The current project aims to use simultaneous acquisition of Functional Magnetic Resonance Imaging (fMRI) and EEG in order to unfold in high spatial and temporal resolutions, respectively the neural modulations induced via T/A EEG-NF. We used real time EEG preprocessing and analysis during the simultaneous T/A EEG-NF/fMRI. A data driven algorithm was implemented off-line to categorize individual scans into responders and non-responders to the EEG-NF practice via a temporal signature of T/A continuous modulation. Comparing the two groups along with their parasympathetic Heart-Rate reactivity profile verified the relaxed state of the responders. Projection of responders variations in the T/A power to the fMRI whole brain maps revealed networks of correlated and inversely correlated activity reflecting induced relaxation, uniquely among responders.\keywords{neuro-feedback, simultaneous fMRI/EEG, theta /alpha ratio, limbic network }

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1 Introduction

It has long been acknowledged that individuals can voluntarily modulate their EEG brain waves via closed-loop neurofeedback (NF) [10]. Early EEG-NF

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protocols for reducing stress were based on the finding that, as individuals become drowsy and deeply relaxed, the dominant frequency of their EEG spectrum commonly shifts from high-amplitude alpha (8-12 Hz) to high-amplitude theta (4-7 Hz) oscillations. The phase when theta activity becomes more dominant than alpha (theta/alpha crossover) is usually associated with loss of consciousness and enter a mental state that would normally be unconscious, "reverie state"[5].Therefore, NF aimed at increasing Theta/Alpha power ratio (T/A-NF) has been applied to enhance a state of deep relaxation, in a range of clinical conditions such as post traumatic stress disorder (PTSD), addiction, epilepsy and attention deficit hyper activity disorder(ADHD)[10,4,6]. Despite promising results in decreasing symptoms even after 30-month follow up [9]the effectiveness of the T/A protocol is still in question[3]. This is possibly related to the obscurity of the underlying neural mechanism of the NF process. One hurdle in revealing the underlying mechanism is the relatively poor spatial resolution of the EEG (cm) mainly for deep brain nuclei which are expected to be involved in modulating emotional states (e.g. amygdala, nucleus accumbens). The aim of the current project is accordingly to use a multi-modal imaging approach in order to categorize individuals EEG-NF attempts by their T/A modulation to reveal related brain networks. We applied EEG-NF and functional-MRI (fMRI) whole brain mapping simultaneously; a method with a superior spatial resolution for functional networks. We also used signal processing of heart-rate variability (HRV) to validate that our T/A performance index results were related to a relaxation state. Fourier transform of the heart rate reveals common high and low frequency peaks of the power spectrum. The high-frequency (0.15 to 0.4 Hz) component of the HRV power spectrum is considered to represent an autonomic parasympathetic response[7]. We hypothesized that modulation of the parasympathetic response would follow the modulation in T/A power time signal.

2 Methods

30 healthy subjects aged 25±3.5 signed an informed consent and participated in a two stage NF experiment; T/A EEG NF training outside the MRI scanner and T/A-EEG NF practice inside the MRI scanner.

EEG-NF Training Outside the Scanner: Sitting comfortably in a quiet dark room with eyes closed subjects were trained to modulate their T/A via EEG-NF for ~15 minutes (Fig 1). The closed-loop feedback consisted of a continuous sound (relaxed piano tune) heard via headphones changing in volume every 3 sec according to the real-time calculation of T/A from three occipital electrodes (Oz, O1, O2)[10]. The feedback criterion was based on a scale of 10 possible values of T/A power ranging from 0.2 to 2 with 10% increase between every two sequential values. Each of these sequential increases corresponded to a specific sound intensity increasing or decreasing inversely proportional to T/A power. Study and feedback rationale were explained to the participants prior to the experiment. Initial auditory volume was adjusted individually according to participants' request. Subjects were instructed to relax very deeply, with reduction in the level of the feedback sound corresponding to achieving relaxation.

EEG-NF Practice in the Scanner: a protocol similar to the training session was applied twice, each time for 15min. EEG was recorded using MRI-compatible 32 electrode (including one electrocardiogram electrode) system[1]. Electrode locations followed the international 10-20 system with sampling rate of 5kHz. Three individualized electrodes out of eight occipital electrodes (OZ, O1, O2, P3, PZ, P4, CP1, CP2) were selected to be the NF electrodes, and used to extract the relevant EEG power for feedback (Fig 1a). Chosen electrodes were the ones that had highest T/A amplitude during the training session. This individualized electrode approach when choosing the NF electrodes helped to increase the efficiency of the feedback. For these three electrodes real time scanning related artifact removal and analysis of the EEG was implemented using software by BrainProducts Inc and robust homemade software. Subjects underwent an fMRI scan simultaneously with the EEG-NF recording.

Scanning Parameters: 3T GE scanner with an 8-channel head coil. fMRI was performed with gradient echo-planar imaging (EPI) sequence of functional T2*-weighted images (TR/TE/flip angle: 3,000/35/90; FOV: 20*20 cm2; matrix size: 128*128) divided into 39 axial slices (thickness: 3 mm; gap: 0 mm) covering the whole cerebrum. Anatomical 3D sequence spoiled gradient echo (SPGR) sequences were obtained with high-resolution 1-mm slice thickness (FOV: 250 mm; matrix: 256*256; TR/TE: 6.7/1.9 ms).

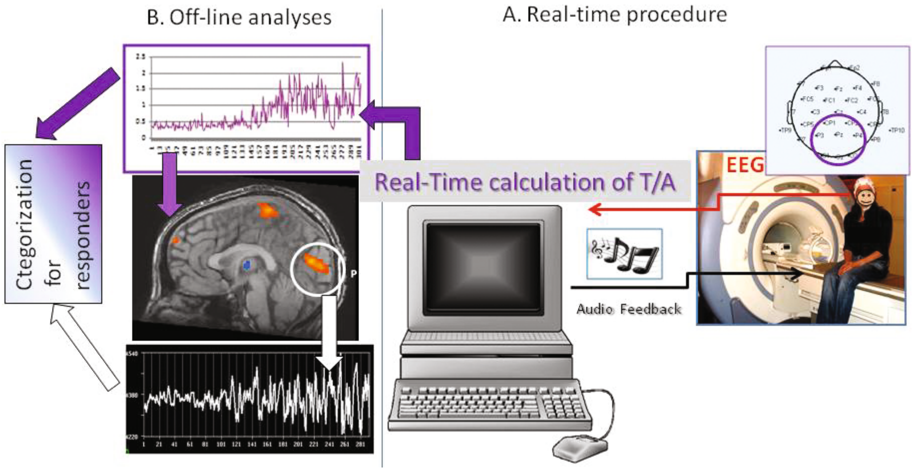


Fig. 1. Schematic description of NF set up. EEG is recorded and analyzed in real time to produce audio feedback to the subject. The purple circle on the right surrounds the eight occipital electrodes from which the three NF electrodes were chosen from after the training session.

Off-line EEG Preprocessing (NF Electrodes): removal of MR gradient artifacts using FASTR algorithm[8] implemented in FMRIB plug-in for EEGLAB[2] and cardio ballistic artifacts using the same FMRIB plug-in. Subsequently, the EEG was down sampled to 250Hz. Next the time-frequency representation of the EEG was calculated using the Stockwell transform[11] with time resolution of one sample and frequency resolution of 0.3Hz. Next, the alpha and theta instantaneous power was extracted from the time-frequency transform as the average power across the relevant bands. Finally, the Theta/Alpha instantaneous power ratio was derived as the sample-wise division of the relevant powers.

Off-line fMRI Preprocessing: by Brainvoyager (Brain Innovation, Maastricht, The Netherlands) included slice timing correction, motion correction, normalization into Talairach space , and spatial smoothing using a 3-mm FWHM Gaussian kernel.

Off-line Heart Rate Preprocessing: HR variability (HRV) signal processing included removal of MR gradient artifacts and detection of ECG R peaks using FMRIB plug-in for EEGLAB. Further irregular beats due to motion artifacts were corrected by visual inspection. The inter-beat intervals were obtained as differences between successive R-wave occurrence times. A linear interpolation was used to obtain an equidistantly sampled time series of RR intervals. Due to motion artifacts, only 10 responders and 10 non-responders were included in the final HR analysis, for which a reliable R peak signal could be detected in all scans.

Off-line Combined EEG-fMRI Analysis

1) Responders vs. Non-responders categorization: A data driven algorithm implemented in Matlab (Mathworks, Framingham, MA) employed the criteria of T/A power increase above 1 ("crossover") for more than a third of the scan to classify each subject's scan as a responder to the NF procedure, or otherwise as a non-responder (Fig2a for responder example).

2) Validation of categorization with a physiological marker (Parasympathetic HRV): Fourier transform was applied to the RR interval time series to obtain the HRV power spectrum. Parasympathetic HRV index was calculated as the power of the high frequency band of the HRV spectrum (0.15-0.4Hz) [7] (Fig 2b,c). Elevation of this parasympathetic HRV index has been linked to relaxation state [7]. We used correlation between the modulation in time of the T/A power ratio and the modulation of the Parasympathetic power to validate the relaxed state of the responders. For 10 subject scans in the responders group and 10 subject scans from the non-responders group, both signal time courses (the power modulation over the time of the scan of T/A and the high frequency band of the HRV spectrum) were divided into seven equal time intervals and averaged over each interval creating a seven points vectors. For each individual we correlated the seven points HRV & T/A vectors. Two sample t-tests were performed between the correlation values of the two groups. (see Fig 2c for one subject example).

3) T/A modulation and related brain networks: a) Characterization of T/A-NF (High vs. Low): In order to reveal brain networks related to the T/A modulation, for responders we identified T/A power time interval corresponding to achieving increased T/A and time interval corresponding to not achieving such as increase. The length of the window interval (20 TRs) was chosen to include continuous power level over the subjects' varied responses. For this purpose we used a sliding window approach with a window of 20 TRs and overlap of 1 TR applied on the individual bands power time course of the responders group. The bands power in each time interval (20 TRs) was averaged, to find the highest and lowest intervals of each band and ratio power corresponding to NF-response and NF-no-response for every scan. (Fig 2c). **b) Brain network - individual and group analysis:** To probe the spatial signature of the individual scan classification, we used three General Linear Model (GLM) analyses with alpha, theta and theta/alpha ratio regressors. Each GLM regressor corresponded to the continuous alpha, theta or T/A power in high and low power segments as defined in the previous step, convolved with hemodynamic response function. Three group random effects analyses of comparison between times of response and non-response activation maps were carried out for each of the individual level GLMs.

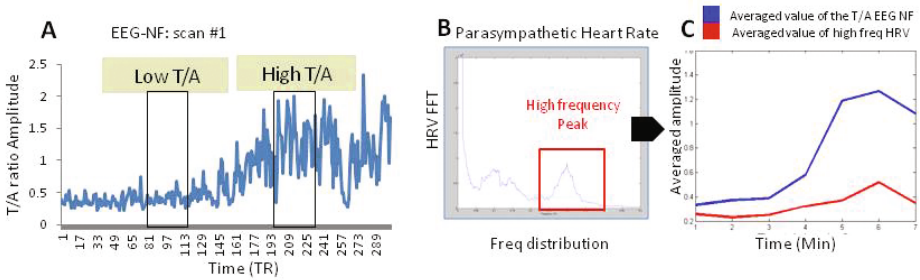


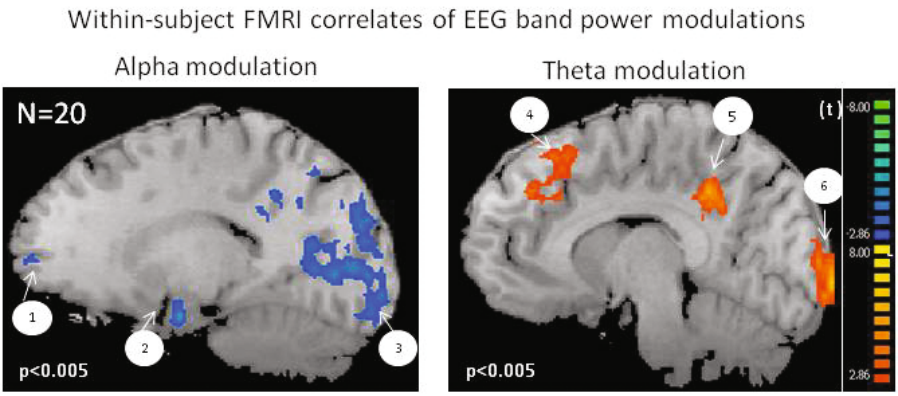
Fig. 2. A. EEG T/A power ratio averaged from the three individual optimal electrodes calculated off-line for subject #1scan1. It is visible that subject # 1was able to increase T/A ratio and the change only started half way into the experiment. Power time course of low and high intervals are demonstrated in black squares. B. Fourier transform of the heart rate revealed the common High and Low frequency peaks of the power spectrum for subject #1. C. Here we demonstrate the correlation between the averaged value of the T/A NF relaxation progression through the experiment for responder subject #1 and the corresponding averaged HF spectrum.

3 Results

Of-line Combined EEG-fMRI:

1) EEG analysis revealed two patterns of T/A power modulation: Responders vs. Non-responders categorization: EEG-NF responders (15 subjects, n=20 scans, 5 subjects responded in both scans) who demonstrated a gradual increase in the T/A. 2. EEG-NF non-responders (15 subjects, 5 subjects did not response in both scans) who did not show a T/A increase as defined by the 'crossover' criterion. (Fig 2a responder T/A power time-course example).

2) Validation of categorization with a physiological marker: As expected, t-test between the two groups correlations of the T/A modulation with the corresponding parasympathetic HRV modulation was significant confirming that the responders indeed entered a relaxed state ($p < 0.0001$) (Fig 2 for one subject example).



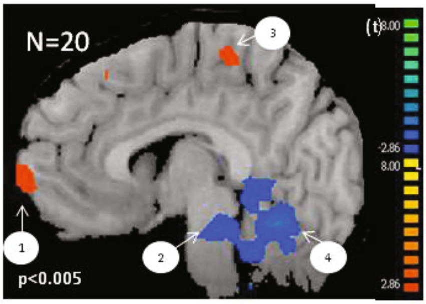
Selected peaks of activation, p<0.0001

Region	Side	x	y	z	T value
Theta Positive					
Posterior cingulate cotex	Right	3	-42	28	5.9
Medial prefrontal cortex	Right	9	28	43	4.5
Primary visual areas	Right	9	-96	-1	6.18
Alpha Negative					
Visual cortex	Left	-11	-73	-4	6.2
Ventromedial PFC	Right	6	65	8	6.3
Amygdala	Left	-18	-4	-17	4.44

Fig. 3. GLM group analysis - response vs. no-response segments. Salient brain areas can be identified, including prefrontal, vision and limbic areas. A) Alpha: 1) ventromedial PFC 2) amygdala 3) visual cortex B. Theta: 4) primary visual cortex 5) posterior cingulate cortex 6) medial prefrontal cortex (For visualization $p<0.005$). Table; peak of activation coordinates of selected areas ($p<0.0001$, uncorrected).

3) Characterization of T/A NF- fMRI related brain networks: fMRI RFX analysis using a contrast of High vs. Low periods of Theta, Alpha or T/A power modulation revealed three specific networks of activation respectively (Fig 3 and Fig 4). Specifically, the activity of a network of cortical and subcortical areas involved in sensory, attention and emotion regulation (e.g. visual cortex/ anterior prefrontal cortex /amygdala, Fig 3a) was inversely correlated to alpha

Within-subject FMRI correlated of EEG T/A ratio changes



Selected peaks of activation, p<0.0001

Region	Side	x	y	z	T value
Positive					
Sup Motor Area	Left	-6	-14	59	5.5
Medial PFC	Right	2	64	8	4.44
Negative					
Cerebellum	Left	-2	-42	-14	6.3
Brainstem	Right	2	-25	-21	4.87

Fig. 4. GLM group analysis – response vs. no-response segments: Salient brain areas for Theta/Alpha ratio correlated activity can be identified. 1) Medial PFC . 2) brainstem 3) Sup Motor Area 4) cerebellum (For visualization $p<0.005$). Table on the right; the peak of activation coordinates of selected areas ($p<0.0001$, uncorrected).

power. The activity of a network of attention allocation areas (medial prefrontal cortex /posterior cingulate, Fig 3b) was positively correlated to increased theta band power.

Lastly, increased T/A in the responders revealed a network of correlated and inversely correlated activity in cortical and deep cortical areas involved in emotional regulation (e.g. anterior prefrontal (BA10)/visual /pre motor/ brainstem, Fig 4).

4 Discussion

The aim of this paper was to use multi-modal imaging approach to categorize individuals EEG-NF attempts by their T/A modulation for revealing related brain networks. Overall our results demonstrate the advantage of considering both temporal and spatial signatures of T/A modulation for classifying a responsive EEG-NF pattern. Heart variability analysis reflects the individual's relaxed state and thus validated the response/non-response categorization. The comparison of the self modulated T/A between response time vs. non-response time revealed brain networks including deep structures, closely related to achievement of relaxation state guided by the EEG-NF practice. Future approaches in improving individual classification will focus on robust machine learning algorithms with the aim of improving the identification ability of mental state performance. We presume that better understanding of the neural mechanism underlying the T/A NF process might help to optimize the neurofeedback procedure at the individual level and thus will increase its specificity per disorder.

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