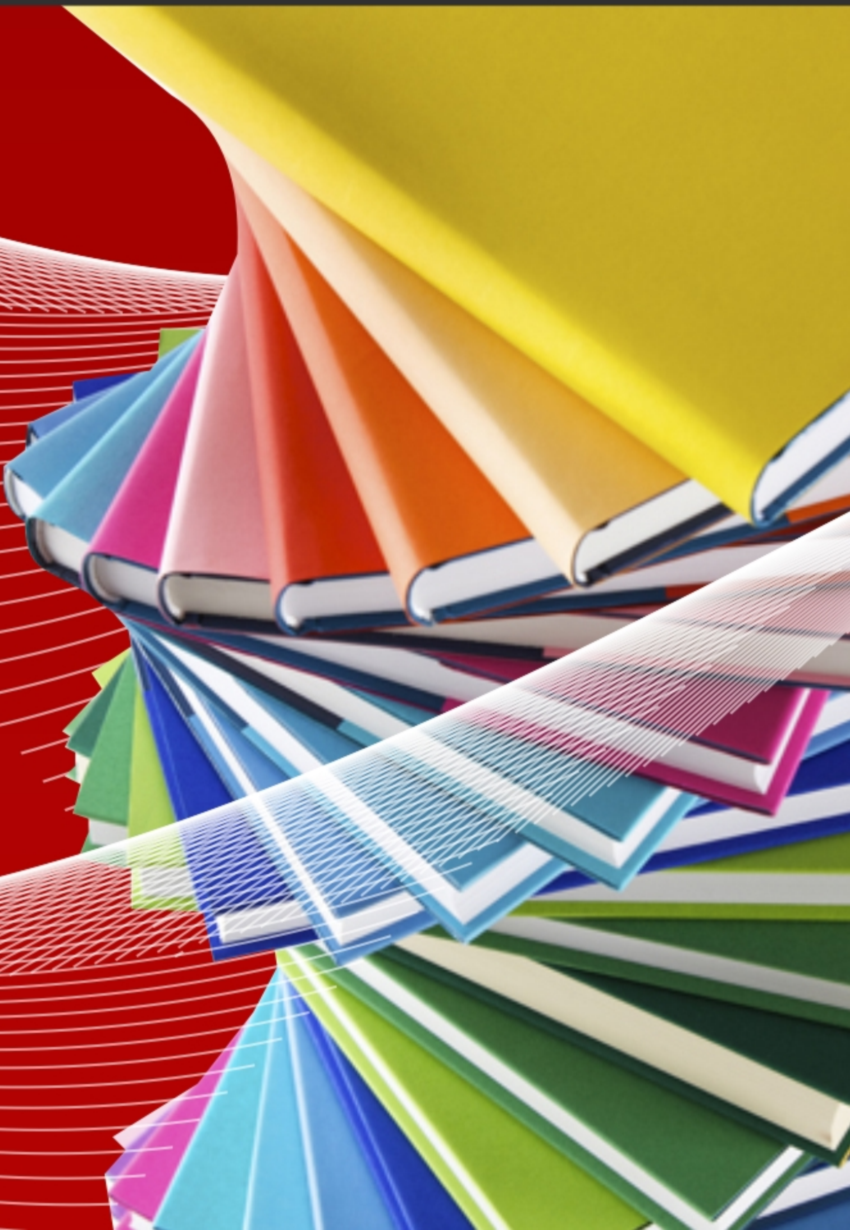
澳門大學
UNIVERSIDADE DE MACAU
UNIVERSITY OF MACAU

# Outstanding Academic Papers by Students
# 學生優秀作品



# INDIVIDUAL ALPHA PEAK FREQUENCY NEUROFEEDBACK TRAINING IMRPOVES COGNITION: A SHAM-CONTROLLED STUDY IN HEALTHY ADULTS

By

**Benzheng Li, Benzene**
**D-B3-2728-3**

Final Year Project Report submitted in partial fulfillment
of the requirements for the Degree of

**Bachelor of Science in Electrical and Computer Engineering**

**2017**

**Faculty of Science and Technology**
**University of Macau**

## Bachelor's Thesis (or Final Report of ECEB420 Design Project II)

In presenting this Final Report of Design Project II (ECEB420) in partial fulfillment of the requirements for a Bachelor's Degree at the University of Macau, I agree that the **UM Library** and **Faculty of Science and Technology (FST)** shall make its copies available strictly for internal circulation or inspection. No part of this thesis can be reproduced by any means (electronic, mechanical, visual, and etc.) before the valid date (usually less than 3 years) limit listed below. Copying of this thesis before the valid date from other parties is allowable **only** under the prior written permission of the author(s).

Printed name: BENZHENG LI, Benzene

Signature: ______________________

Student number: D-B3-2728-3
Date: May 12th, 2017
Reliable Contact information (address, tel. no., email, etc.) of author:
Email: LBenzheng@gmail.com
Adress: 12-A, Residential Courtyard, No.204 Wenchang St., Yinchuan, China

Valid date until May 12th, 2019

## DECLARATION

I declare that the project report here submitted is original except for the source materials explicitly acknowledged and that this report as a whole, or any part of this report has not been previously and concurrently submitted for any other degree or award at the University of Macau or other institutions.

I also acknowledge that I am aware of the Rules on Handling Student Academic Dishonesty and the Regulations of the Student Discipline of the University of Macau.

Signature : ______________________

Name : BENZHENG LI

Student ID : D-B3-2728-3

Date : May 12th, 2017

## APPROVAL FOR SUBMISSION

This project report entitled "**Individual alpha peak frequency neurofeedback training improves cognition: a sham-controlled study in healthy adults**" was prepared by Benzheng Li (D-B3-2728-3) in partial fulfillment of the requirements for the degree of Bachelor of Science in Electrical and Computer Engineering at the University of Macau.

Endorsed by,

Signature :

Supervisor : Prof. Feng WAN

Co-Supervisor(s) : Prof. Agostinho Rosa

**ACKNOWLEDGEMENTS**

This work was supported in part by FCT SFRH/BSAB/1101/2010 and PEst-OE/EEI/LA0009/2011 grants and the Macau Science and Technology Development Fund under grant FDCT 036/2009/A and the University of Macau Research Committee under grants MYRG139(Y1-L2)-FST11-WF and MYRG079(Y1-L2)-FST12-VMI.

# ABSTRACT

As reported in many studies, resting individual alpha peak frequency (iAPF) had been shown to positively correlate with cognitive performances. This study aimed to enhance cognition by up-regulating iAPFs in the eyes-closed condition using neurofeedback training (NFT). Before and after all training sessions, cognitive abilities were assessed by the mental rotation and n-back tests. Twenty-eight healthy adults were randomly assigned to a neurofeedback group, where real-time feedbacks of iAPFs were given, and a sham group, where irrelevant placebo feedbacks were provided. Results suggested that iAPFs and performance of the mental rotation test had been significantly increased in the neurofeedback group, while no significant changes were observed in the sham group. The finding suggested the effectiveness of the iAPF NFT on enhancement of cognitive performance.

# TABLE OF CONTENTS

## LIST OF TABLES/FIGURES

# CHAPTER 1 INTRODUCTION

## 1.1 Background

The notion that brain activities detected by the electroencephalogram (EEG) are related to the measure of intelligence and cognition has been reported long since the invention of EEG. (Grandy, 2013b) Among various kinds of brain activities, alpha activity, a prominent EEG feature, has been reported to be related to cognitive ability. (Klimesch, 1996, 1999, 2006)

The individual alpha peak frequency (iAPF), also called peak alpha frequency (PAF) or individual alpha frequency (iAF) refers to the frequency with the peak amplitude within the standard alpha range on the EEG spectrum, in addition, it is highly heritable and has large individual differences commonly between 7 to 13 Hz (Posthuma, 2001). More importantly, the iAPF is the anchor point to determine the individual alpha band and has been shown to positively correlate with cognitive performance, inversely correlate with ages of adults, and is especially lower in individuals with Alzheimer's disease. (Klimesch,1997, 1999). However, the previous studies indicate that the iAPF is a stable neurophysiological trait marker and does not differ after the improvement of cognitive performance under long-term cognitive training. (Grandy, 2013a) A pilot neurofeedback study provided three cases of up-regulated iAPFs in the elderly and observed the improvement of cognitive performance compared to controls. (Angelakis, 2006) Due to the vague and uncertain causality between iAPF and cognition, further investigations regarding the effects on cognitive performance caused by the change of iAPF are required. An experiment with comparable sample size to investigate whether enhancement in cognition goes along increased iAPFs shall be needed.

## 1.2 Neurofeedback training

Neurofeedback, a type of biofeedback that commonly use EEG, is an operant conditioning method to realize the self-regulation of certain brain activities that underlie a specific behavior or pathology. During neurofeedback training, a certain neural activity is measured and presented to participants in real time using visual, auditory, haptic or another representation, to facilitate self-regulation. (Sitaram, 2016)

A neurofeedback training system using eyes-closed iAPF as the training protocol was built and implemented to realize the up-regulation of iAPFs of parietal and occipital regions for the inducing of intra-individual iAPF changes. To eliminate irrelevant factors and minimize differences resulted from placebo or nocebo effects, pseudo-neurofeedback training was implemented in the experiment as the sham control. The behavior performance, i.e. cognitive performance in this study, was assessed by the mental rotation test and working memory tests, including a 1-back and 3-back tests.

Because the power of the alpha peak is largely depressed during the eyes-open condition (Klimesch, 1999; Hanslmayr, 2005), it is more feasible to train iAPFs in the eyes-closed condition, which causes inapplicability of visual feedbacks. Most studies employed auditory feedbacks for the eyes-closed condition. A few existing NFT studies use haptic feedback and they are mostly related to the motor imagery and mainly focus on the neurorehabilitation of stroke patients. (Gharabaghi, 2014) In contrast to auditory feedbacks, haptic feedbacks are relatively simple and can avoid advanced cognitive functions during the training. Besides, the feasibility and effectiveness of applying haptic feedbacks in neurofeedbacks for healthy subjects still lack of investigation.

### 1.3. Hypotheses and Finding

The general hypotheses of this study were: iAPFs can be self-up-regulated neurofeedback training via haptic feedbacks in the eye eye-closed condition, and the increase of the iAPF induces the enhancement of the cognitive performance. Results presented in this study showed that iAPFs and performance of the mental rotation test had been significantly increased in the neurofeedback group only. Meanwhile no corresponding significant changes were displayed in the sham group. The finding suggested the effectiveness of the iAPF NFT on enhancement of cognitive performance, and implied the evidence to determine the causality between iAPFs and cognition.

# CHAPTER 2 METHOD

## 2.1 Participants

A total of 31 healthy subjects (21 males and 10 females) recruiting from the same collage participated in this study. Participants were randomly divided into the neurofeedback training group (NFT group), and the pseudo-neurofeedback training sham control group (sham group). Data from three participants had to be discarded, including two participants who didn't comply with instructions and one participant whose data were corrupted and incomplete due to technical problems. Hence, the final sample consisted 28 subjects (18 males and 10 females, age: 21.5±3.06 years) remained for future statistical analyses and consisted of 15 subjects in the NFT group (11 males and 4 females, age: 21±3.34 years) and 13 subjects in the sham group (7 males and 6 females, age: 20.92±2.72 years).

A randomized and blinded trial, where participants did not know the division of groups nor which group they belonged to, was performed. Differences between two groups were in neurofeedback training sessions only. Subjects in the NFT group received real feedback based on their real-time iAPFs. In contrast, sham group got pseudo feedback, a playback of a feedback recording from a successfully trained subject in NFT group.

All participants were healthy, reported no history of neurological or psychiatric disease, had normal or corrected vision, and were all right-handed, except one left-handed subject in the NFT group. Subjects were medication-free during experimental days and had sober mental states at the beginning of the experiment each day. Participants gave written informed consents in advance and then received a fixed amount of monetary reward after the completion of all procedures. To avoid placebo effects related to cognitive-training (Foroughi, 2015), participants were uninformed of the correlation between cognitive performance and trained protocol. Fatigue levels were evaluated at the end of the experiment by questionnaires (Chalder Fatigue Scale, Chalder, 1993), and subjects were instructed to assess their fatigues by comparing the mental states before and after experiments.

## 2.2 Experiment Design

The experiment consisted of eight sections within continuous two days. (Fig.1) In the first day, a resting EEG baseline was recorded, then cognitive tests were arranged to assess the pre-training cognitive performance. Next, participants completed a NFT session composed of five 3 minutes training blocks and repeated baseline recording after training. In the same time of the next day, a resting EEG baseline recording was conducted, followed by another NFT session consisted of five training blocks also of 3 minutes and the last EEG baseline recording. Subsequently, the post-training cognitive performance was assessed by the same cognitive tests. After the post tests, each subject filled out a questionnaire to report fatigue levels, self-rated cognition ability, inverse side effects, and effective mental strategies used during NFT sessions.

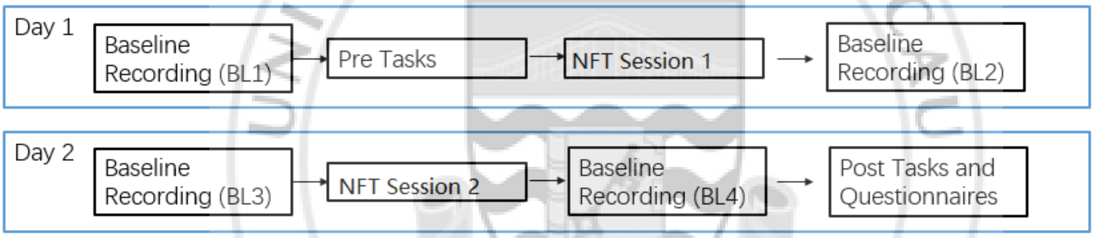



Fig.1 Brief flow chat of the iAPF NFT experiment

## 2.3 EEG Acquisition

EEG was recorded from 16 Ag/AgCl electrodes placed in an EEG cap based on the International 10-20 system (Jasper, 1958) (Fig.2). Used positions were O1, Oz, O2, P3, Pz, P4, C3, Cz, C4, T3, T4, F7, F3, Fz, F4, and F8. All channels were referenced to the A1 and grounded to the FP2. Impedances of each electrode were kept below 10 kΩ. Signals were amplified by a USB biosignal amplifier (g.tec Inc., Graz, Austria) with a sampling rate of 256 Hz and a band-pass filter from 2 to 30 Hz and a 50 Hz notch filter to avoid power line interference. The EEG measurement was carried out in a windowless quiet dim room, in which subjects were seated comfortably in an arm-chair.

The baseline recording consisted of two blocks, one with eyes-open (EO) condition and the other one with eyes-closed (EC) condition. Each block consisted of four epochs of 30 s separated by 10 s rest. Subjects were instructed to open or close eyes during recording. For the eyes-open condition, subjects were instructed to gaze at a blank screen of a monitor and to avoid frequent blinking. For the eye-closed condition, subjects were told to avoid the rolling of eyeballs.

During the cognitive tests, EEG was recorded and synchronized to the progress of tests through a photosensitive device for the future analyses. The photosensitive device detected the optical signal from the monitor and send the digital input to the USB biosignal amplifier. The synchronizing signal was recorded at the time whenever the stimulation appeared and the subject reacted.

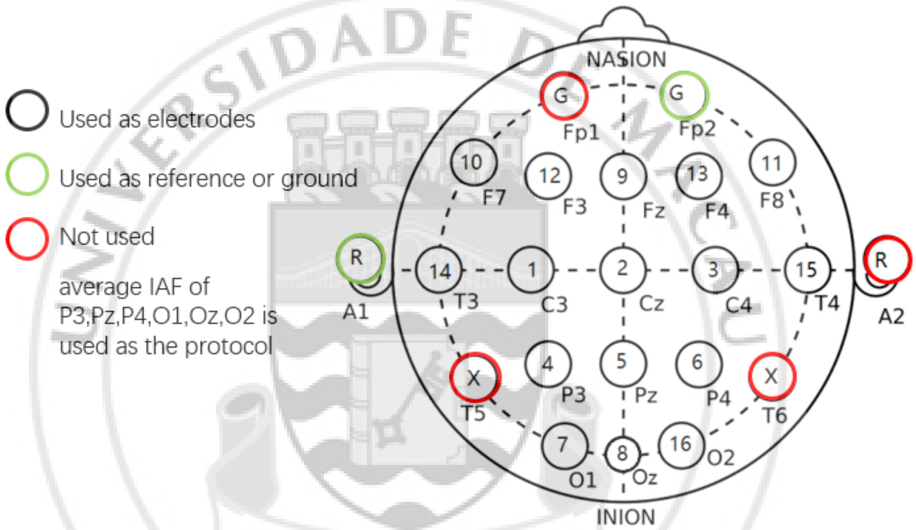



Fig.2 The 10-20 system with labeled electrodes related to the EEG recording

### 2.4 Neurofeedback training and iAPF protocol

The NFT protocol was set as the mean of iAPF obtained from P3, Pz, P4, O1, Oz, and O2 in the eyes-closed condition. The power of the alpha peak is typically highest at parietal regions during eyes-closed condition and it is depressed during the eyes-open condition. (Klimesch, 1999; Hanslmayr, 2005) Besides, parieto-occipital regions were commonly used in neurofeedback studies related to individual alpha rhythms. (Zoefel, 2011; Angelakis, 2007) For training in the eyes-closed condition, a haptic feedback was utilized.

A NFT session consisted of three blocks, which contained three epochs of 60 s neurofeedback training segmented by 10 s rest. During the training blocks, subjects were instructed to sit in a comfortable position, close eyes, and put their two index figures on a haptic feedback device placed on the table. Subjects were informed that the vibration amplitude changed depended on their brain activity, and told to make the vibration as strenuous and everlasting as possible. The feedback was induced by a haptic feedback device, which was mainly built by two vibration motors and controlled by the amplified output of the computer sound card. The vibrating frequency was fixed at 100 Hz, and the vibrating amplitude was moderate and has been tested by each subject before NFT sessions to ensure that different levels were distinguishable during training.

A sliding Fast Fourier Transform (FFT) algorithm (2 s hanning window, 95% overlap, 6 s zero padding) was used to calculate the power spectrum density of the EEG signal. To obtain a real-time computation of iAPF with a fluent refresh rate and a sensitive frequency resolution, the EEG signal was buffered, updated every 100 ms, i.e. 95% overlapped sliding hanning window, and processed by padding zeros and extending the length to 2048 sampling points, i.e. 0.125 Hz frequency resolution under the 256 Hz sampling rate. Then the obtained power spectrum was smoothed by moving average method using a Savitzky–Golay filter with second-order polynomial smoothing, which can preserve important features of alpha peaks such as maxima, minima and widths. (Martinez, 2007) The iAPF was computed as the peak frequency of the smoothed peak in the alpha band between 7 to 13 Hz. Although usually the iAPF could be computed from all training channels in the eyes-closed condition during training, occasionally alpha peak could be indistinct in the alpha band due to artifacts and interferences. Therefore, the iAPF wasn’t computed from alpha peaks with low relative amplitude, double peaks, or the peak frequency located close to the boundary of mentioned interval. These channels without iAPF were omitted while taking the average from six training channels. If none of training channels provided iAPF, the updated value would be kept as the assigned threshold iAPF during training.

The feedback parameter was determined as the incensement of the computed mean iAPF exceeding the threshold value, and it was cumulated in a heap conserved for 500 ms. The average value of the heap was reflected on the amplitude of vibration feedback perceived by the subject. The threshold value for the first NFT session each day was determined by the previous EC baseline. The threshold values for the subsequent NFT sessions were adjusted based on the performance of the last sessions. The percentage of the time when the feedback parameter was above the threshold value were counted after each session. The threshold value of the next session would be lifted by 0.1 to 0.3 Hz if the percentage exceeded 70%, on the contrary, it would be decreased by 0.1 to 0.3 Hz if the percentage was lower than 30%. (Wenya Nan, 2012)

## 2.5 Cognitive tests

Cognitive performance was assessed by a mental rotation test and n-back tests. The assessment started with n-back tests, including one session of 1-back test and two sessions of 3-back test, and ended with two sessions of mental rotation test. This order of tests was identical in the first day and the second day. Participants were finely instructed and had a few minutes for exercise before each test. Stimuli of tests were displayed on a 24-inch liquid crystal display monitor placed about 60 cm in front of subjects with 82% color gamut and a refresh rate of 60 Hz. Subjects were required to react after stimuli by pressing corresponding buttons on a keyboard with their dominant hand.

### *2.5.1 Mental Rotation Test*

The mental rotation test utilized in this study was programed by reference to two versions of mental rotation tests, IST70 (Amthauer, 1970; Hanslmayr, 2005) and A3DW (Adaptiver dreidimensionaler Wuerfeltest) (Gittler, 2007). This test was completed 2 sessions each day, and 15 trials in every session with a short break in between. Each trial began with a fixation cross showed for 3 s, and then two cubes were displayed for 8 s. A red bar appeared on the center of the screen as a warning signal to remind subjects to response one second before the end of the trial. Subjects had to indicate whether two cubes were matching and react as fast and accurate as possible. For congruent pairs (Fig.3.a), two cubes could be convertible into each other, meanwhile, subjects were expected to press a keyboard button with their index fingers. For incongruent pairs (Fig.3.b), two cubes, although had similar pattern on each face, couldn't be convertible into each other, and subjects were expected to press an adjacent button with their middle fingers. Sequences of pairs were pseudo-random with a 50% possibility to present congruent pairs. The cognitive performance was assessed by the reaction time and the accuracy.

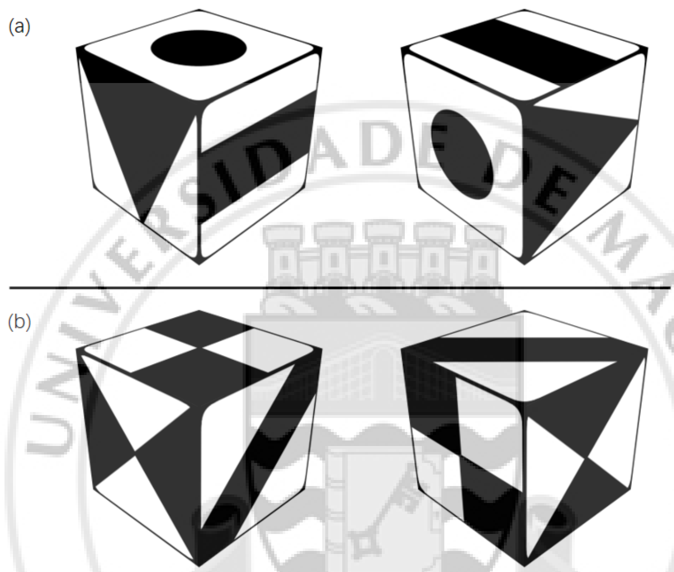



Fig.3 A matching pair (a) and a mismatching pair (b) of cubes in the MRT

### *2.5.2 N-back Tests*

The n-back tests included the 1-back single tests and the 3-back single tests with visuospatial stimuli. The visuospatial stimuli consisted of light blue squares appearing on the black background at one of eight slotted positions around a central fixation cross. (Susanne, 2010; Hockey, 2004) In each day subjects were required to finish three sessions of n-back tests, one session of the 1-back test (28 trials each session) and two sessions of 3-back tests (30 trials each session). Each trial started with displaying a constant fixation cross for 2 s, then a stimulus appeared for 250 ms. During the test, subjects were asked to response by pressing the button with their index finger whenever the current stimulus matched the one (1-back) or three (3-back) positions before in the on-going sequence. (Fig.4) Matching targets were presented following a pseudo-random sequence with a 33% possibility. The cognitive performance was assessed by the reaction time and accuracy, which was computed as the sum of hits (the number of targets – omission errors) and correct rejections (the number of distractors – commission errors) divided by the total number of trials.

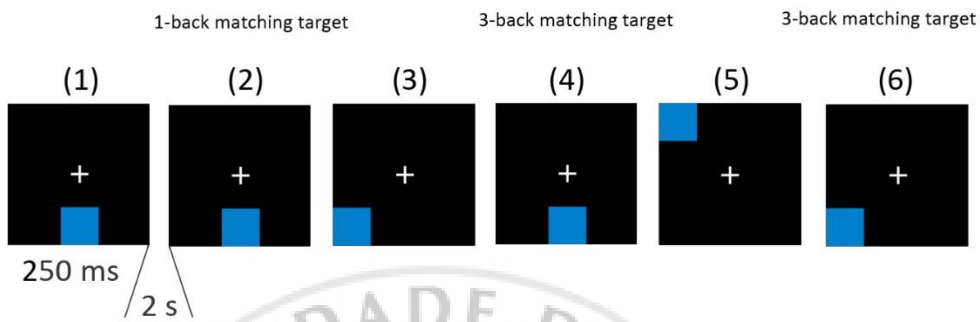



Fig.4 The sequence of stimuli of a visuospatial n-back tests (1-back and 3-back)

## 2.6 Data Analyses

### *2.6.1 EEG Data*

The average of iAPFs taken from P3, Pz, P4, O1, Oz, and O2 was calculated for each subject in each section with EEG recording in the eyes-closed condition, including four sections of resting baselines, two sections of cognitive tests, and two sessions of neurofeedback training. First, sequences of iAPFs were computed by using a sliding FFT (5 s hanning window, 10% overlap) to EEG data recorded from each electrode as the frequency between 7 and 13 Hz with the largest amplitude on the smoothed spectrum. The arithmetic mean of the sequence of iAPFs was regarded as the average iAPF of each recording from each electrode. The overall training iAPF during one session of EEG recording was computed as iAPF from six training electrodes. Initial iAPFs of NFT and sham groups computed from day-1 pre-baselines were compared using independent t-test. Then all obtained iAPFs were fed into a mixed analyses of variance (ANOVA) with within-subjects factor *Time* (6 levels: day-1 pre-baseline, 1st training session, day-1 post-baseline, day-2 pre-baseline, 2nd training session, and day-2 post-baseline), and between-subjects factor *Group* (2 levels: NFT and sham). Paired-sample t-tests were also employed to check the pre-to-post differences in two groups respectively. Besides iAPF, resting upper alpha amplitude (UA) and the long-range temporal correlation (LRTC) in eye-closed condition were calculated by taking average from P3, Pz, P4, O1, Oz, and O2. Upper alpha amplitudes were calculated by taking relative amplitudes of individual upper alpha band, i.e. iAPF to iAPF + 2Hz, on FFT spectra. The Neurophysiological Biomarker Toolbox (NBT, www.nbtwiki.net) were employed to calculate LRTCs in the fixed-band alpha range between 7 to 13 Hz. Identical methods with analyses of iAPFs were used for statistical analyses of UAs and LRTCs.

### *2.6.2 Behavioral Data*

About the behavior performance, reaction time and accuracies were regarded as indicators and computed for statistical analyses. Percentage ratios of hits, correct rejections, omission errors (misses), and commission errors (false alarms) were also computed for detailed performance during behavioral tests. Normality of all above behavioral data were assessed using Shapiro-Wilk test. If the data were normally distributed, independent t-test was applied to compare the initial behavior performance between two groups, and 2 × 2 mixed ANOVA with *Time* (pre-training, post-training) as within-subject factor and *Group* (NFT, sham) as between-subject factor was performed to analyze the neurofeedback training effects. Otherwise, a Mann-Whitney U test was employed to check the initial performances between two groups, and a Wilcoxon signed-rank test was used to evaluate the differences between before and after training for each group separately. Statistical analyses were performed using the Statistical Package for the Social Science ver.20.0 (SPSS Inc., Chicago, IL, USA). A significance level of $p<0.05$ was adopted for all statistical tests.

# CHAPTER 3 RESULTS

## 3.1 EEG RESULTS

The independent t-test revealed that resting iAPFs at day-1 pre-baseline had no significant difference between two groups ($t_{(26)}$ = -1.292, $p$ = 0.208 ; NFT: 10.54 ± 0.65 Hz, SHAM: 10.24 ± 0.57Hz). As shown in Fig.5, the iAPF changed over time for both groups. In line with the training objective, iAPF showed a decrease trend in the sham group but an increase trend in the NF group. Moreover, mixed ANOVA showed a significant main effect of *Time* ($F_{(3.667,\ 95.352)}$ = 6.441, $p < 0.001$, $\eta^2$ = 0.199) and *Group* ($F_{(1,\ 26)}$ = 5.112, $p$ = 0.032, $\eta^2$ = 0.164). Importantly, a *Time* × *Group* interaction was observed ($F_{(3.667,\ 95.352)}$ = 3.522, $p$ = 0.005, $\eta^2$ = 0.119). Post-hoc comparisons showed that only the NF group enhanced iAPF over time ($p < 0.001$). More specifically, multiple comparisons after Bonferroni-correction revealed that iAPF during neurofeedback session and post baseline were significantly higher than pre-baseline for both training days ($p < 0.05$) in the NFT group.

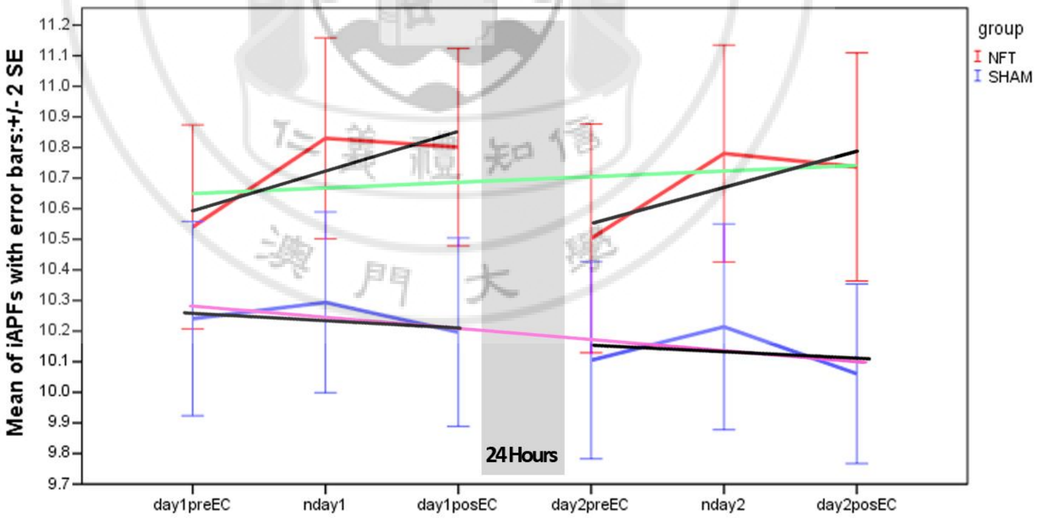



Fig.5 Mean of iAPFs in NFT and sham groups over 6 sections with error bars presenting two times of standard error and trend lines of mean iAPFs (green and magenta lines two-days measures, and black lines for within-day measures).

For UAs and LRTCs, no significant differences in day-1 pre-baseline were found by independent t-tests (UA: $t_{(26)}$ = -0.715, $p$ = 0.481; LRTC: $t_{(26)}$ = -1.802, $p$ = 0.083). Mixed ANOVA revealed neither significant effects of *Group* or *Time,* nor significant *Time* × *Group* interaction ($p < 0.05$ in all cases). This suggests that results in terms of changes of UAs and LRTCs would not be taken in to account.

### 3.2 Behavioral results

#### *3.2.1 Mental rotation test*

For ensuring that two groups had similar initial performances, an independent t-test was performed for differences in pre-training performance between NFT group and sham group. The test revealed no significant differences in initial performance for accuracy ($t_{(26)}$ = 0.847, $p$ = 0.405 ; NFT: 74.4±13.4 %, SHAM: 78.9±14.9%), and reaction time ($t_{(26)}$ = - 0.687, $p$ = 0.498 ; NFT: 5.33±0.72s, SHAM: 5.09±1.12s).

After performing mixed ANOVA on the accuracy of the mental rotation test before and after training, results revealed no effects of *Time* ($F_{(1, 26)}$ = 3.074, $p$ = 0.091, $\eta^2$ = 0.106) and *Group* ($F_{(1, 26)}$ = 0.085, $p$ = 0.744, $\eta^2$ = 0.003), but showed a significant *Time* × *Group* interaction ($F_{(1, 26)}$ = 8.235, $p$ = 0.008, $\eta^2$ = 0.241). Paired-sample t-test showed a significant accuracy enhancement in the NFT group ($t_{(14)}$ = - 3.329, $p$ = 0.005), and no significant differences in the sham group ($t_{(12)}$ = 0.780, $p$ = 450).

For the reaction time, significant effects of *Time* was observed only ($F_{(1, 26)}$ = 17.821, $p$ < 0.001, $\eta^2$ = 0.407). Neither effects of *Group* ($F_{(1, 26)}$ = 0.379, $p$ = 0.544, $\eta^2$ = 0.014), nor any significant interaction ($F_{(1, 26)}$ = 0.02, $p$ = 0.696, $\eta^2$ < 0.001) were found. By using paired t-test, reaction time of both groups were significantly reduced after training sessions (NFT: $t_{(14)}$ = 3.094, $p$ = 0.008 ; SHAM: $t_{(12)}$ = 2.893, $p$ = 0.014).

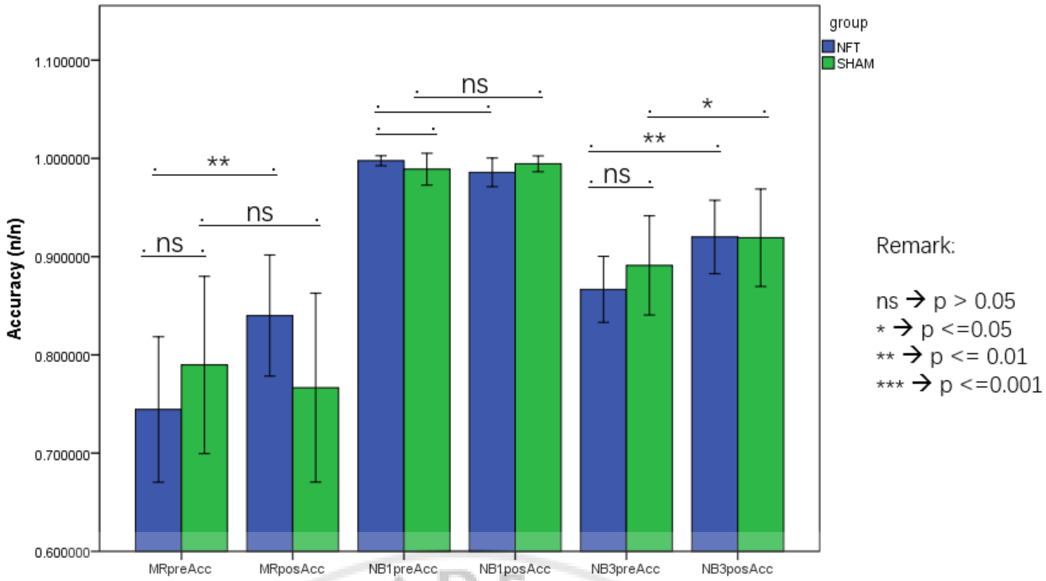



Fig.6. Pre-training and post-training accuracies and statistical significances of mental rotation tests (left), 1-back tests (middle), and 3-back tests (right)

### *3.2.2 N-back tests*

Shapiro-Wilk normality tests showed non-normal distribution of performances in both 1-back and 3-back tests. Therefore, non-parametric tests were used in this section. Mann-Whitney U test revealed that all initial performances of 1-back and 3-back tests between two groups were not significantly different. ($Z < -0.05$, $p > 0.1$ for accuracy, reaction time, percentages of hits, correct rejections, omission errors, and commission errors in 1-back and 3-back tests).

For 1-back test, no significant results were obtained by the Wilcoxon signed-rank test in both groups. (all indicators: $Z < -0.90$, $p > 0.1$ for NFT group; $Z < -0.44$, $p > 0.15$ for sham group). For 3-back test, accuracy and reduced reaction time were significantly enhanced in both groups (Accuracy: NFT: $Z = -2.639$, $p = 0.008$; SHAM: $Z = -2.298$, $p = 0.022$) (reaction time: NFT: $Z = -2.953$, $p = 0.003$; SHAM: $Z = -2.83$, $p = 0.005$). Percentage of hits (%Hits) were significantly increased in both groups (NFT: $Z = -2.784$, $p = 0.005$; SHAM: $Z = -2.825$, $p = 0.005$). No differences in percentage of correct rejections (%C.R.) were found in both groups ($Z < -0.764$, $p >$ 0.84 for both groups). Percentages of omission error (%Misses), and commission error (%F.A., False Alarms) were significantly decreased in the NFT group (%Misses: $Z = -$

2.386, $p$ = 0.017; %F.A.: $Z$ = -2.294, $p$ = 0.022), and had no differences in the sham group (%Misses: $Z$ = - 1.423, $p$ = 0.155; %F.A.: $Z$ = - 1.274, $p$ = 0.203).

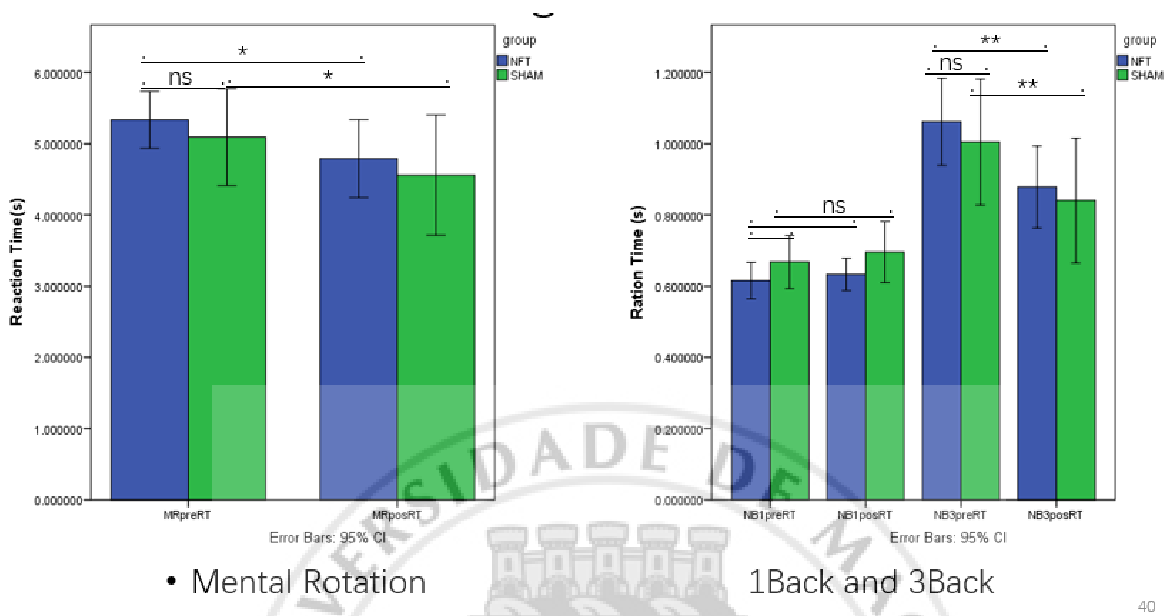



Fig.7 Pre-training and post-training reaction times and statistical significances of mental rotation tests, 1-back tests, and 3-back tests

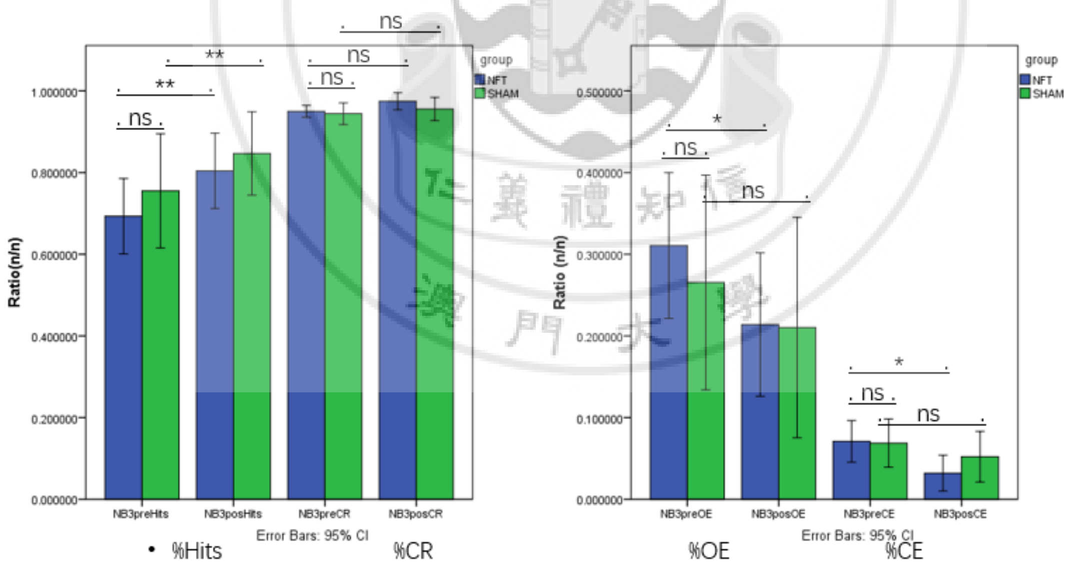



Fig.8 Pre-training and post-training %Hits, %C.R., %Misses (%OE), %F.A.(%CE) and statistical significances of 1-back tests, and 3-back tests

Tab.1. Significant improvement and worsening per group in EEG features, mental rotation test and n-back test

| | NFT group | sham group |
|---|---|---|
| **EEG feature** | | |
| IAPF | + (***) | |
| UA | | |
| LRTC | | |
| **Mental rotation test** | | |
| Accuracy | + (**) | |
| Reaction time | +(*) | +(*) |
| **1-back test** | | |
| Accuracy | | |
| Hits | | |
| Correct Rejections | | |
| False Alarms | | |
| Misses | | |
| Reaction time | | |
| **3-back test** | | |
| Accuracy | +(**) | +(*) |
| Hits | +(**) | +(**) |
| Correct Rejections | | |
| False Alarms | +(*) | |
| Misses | +(*) | |
| Reaction time | +(*) | +(*) |

"+" : improvement; "-" worsening,
"*" : p <=0.05; "**" : p <= 0.01; "***" : p <=0.001

### 3.3 Questionnaires

#### *3.3.1 Self-rated cognitive ability*

Initial self-rated cognitive ability scores of two groups before experiments were not significantly different checked by Mann-Whitney U test ($Z$ = -0.72, Exact $p$ = 0.496), and Wilcoxon signed-rank test revealed no differences between self-rated cognitive ability before and after experiments in both groups ($p$ >0.1 for two groups).

#### *3.3.2 Fatigue*

Subjective rated fatigue scores exhibited that most subjects didn't get tired of the experiment obviously. Mean fatigue levels assessed by the Chalder Fatigue Scale computed from 20 out of 28 subjects were close to or better than the level stands for "no more than usual". Three subjects in the NFT group reported that they had problems with sleepiness much more than usual. From statistical sense, the Mann-Whitney U test showed that there was no significant difference between fatigue levels in two groups ($Z = -1.537$, Exact $p = 0.142$).

### *3.3.3 Adverse side-effects*

No adverse side-effects were reported from more than half of participants (67.8%). Besides, the most frequently reported adverse side-effects after the experiment were itch from six subjects (17.8%), including five subjects from the NFT group and one subject from sham group. Two subjects, one received NFT and one received pseudo-NFT, reported that they suffered from slightly headache during short periods. As existing study reported, the adverse side effects of neurofeedbacks are as few, rare, and quickly remediable (Rogel, 2015). Although, it has also been reported that the pseudo-neurofeedback training could cause heavier side effects due to the learning helplessness feeling (Escolano, 2014). In this study, the Mann-Whitney U test revealed no differences between two groups in the rating of side effects ($Z = -0.879$, Exact $p = 0.467$).

### *3.3.4 Mental strategies*

Subjects from both groups were asked to write down the mental strategies with good efficacies during the neurofeedback training or pseudo-neurofeedback training. Recorded effective strategies were categorized into three types in emotional valences, i.e. positive (pleasant), neutral, and negative (unpleasant). Positive types commonly include friends, families, entertainments, love, etc. Neutral types contained calculation, recitation, counting numbers, etc. Negative type consisted of sorrow, anger, quarrel, phobia, etc. In the NFT group, 11 subjects (73.3%) listed positive strategies, 9 subjects (60%) listed neutral strategies, and 1 subjects (6.7%) listed negative strategies. In the sham group, 7 subjects (53.8%) listed positive strategies, 7 subjects (53.8%) listed neutral strategies, and 4 subjects (30.8%) listed negative strategies. In contrast, although mostly subjects were inclined to use pleasant mental strategies during training, more pleasant strategies and less unpleasant strategies were provided by subjects who received real neurofeedbacks than subjects received irrelevant feedback. It's implied that positive mental strategies could be more effective in the neurofeedback training for up-regulating iAPF among parietal and occipital regions.

# CHAPTER 4 DISCUSSION

## 4.1 Effectiveness of the iAPF NFT

As expected, this study demonstrates intra-individually increased iAPFs accompany by promoted cognitive performance in mental rotation tests and 3-backs. Overall, iAPFs of subjects in the NFT group significantly went up during the training sessions, and showed a significant increase, in resting baselines compared with the sham group, which showed no significance in iAPFs. By 2-days neurofeedback training, iAPFs were raised about 0.21 Hz in average for baselines, and about 0.26 Hz during training sessions. Remarkably, three subjects in NFT group had resting iAPFs raised over 0.5 Hz up to 0.7 Hz. However, iAPFs showed a distinguishable resilience after a day, and in the second training day, they commonly dropped back to the similar levels as the initial baselines. Compared with the pilot study that performed eyes-open iAPF neurofeedback in 3 elderlies reported, iAPFs went up about 0.6 Hz after 15 1-hour sessions and stabilized about that level (Angelakis, 2006). Healthy adults in this study exhibited greater flexibility, as well as resiliency, of iAPFs. On the other side, iAPF changes were more heterogeneous in the sham group, where iAPFs of two subjects declined about 0.8 Hz, and iAPFs of two subjects raised about 0.5 Hz after two pseudo-neurofeedback sessions. Besides, the sham group showed much greater variances of percentage changes of iAPFs during training and after training.

With effects of training and placebo, both NFT group and sham group displayed enhanced cognitive performance in speeds of the mental rotation test and 3-back test, and the accuracy of 3-back test. Nevertheless, the significant improvement of the accuracy in mental rotation test and the decreased percentages of false alarms and misses in 3-back test were presented in the NFT group only.

## 4.2 Alpha oscillations and cognitions

Many existing studies worked on finding out relationships between performance of mental rotation tests and modulated individual alpha band power by different approaches, such as neurofeedback training (Hanslmayr, 2005; Zoefel 2011), repetitive transcranial magnetic stimulation (rTMS) (Klimesch et al., 2003), and transcranial alternating current stimulation (tACS) (Kasten, 2017). In spite of the fact that the training protocol in this study is the iAPF and no significant alpha band power changes were found, results of behavior performance showed a remarkable comparability to some extents. Accuracies of mental rotation tests were increased after using different mentioned approaches, but no significant improvement of reaction speed was found. This similarity may imply that the modulation of alpha activity does not have effects on the speed of reactions in mental rotations.

### 4.3 Importance of using sham-controlled design

Since the neurofeedback emerged in the 1970s, significant controversy exists concerning the development of EEG neurofeedback particularly for clinical usages in the field of psychiatry and neurology. (Coben, 2011; Micoulaud-Franchi, 2015) Opinion appears to be sharply divided regarding to the efficacy of neurofeedback training: one school of thought considers neurofeedback to be effective, whereas the other school of thought does not consider neurofeedback training to have any effects in clinical practices. (Micoulaud-Franchi, 2015)

Many existing neurofeedback studies have methodological weaknesses due to the absence of the sham-controlled design. Neurofeedback may offer a potent psychosocial intervention and represent a super-placebo compared with other clinical domains such as psychopharmacology (Thibault, 2017). The general goal of neurofeedback is to effectuate a behavioral modification by modulating brain activity. (Coben, 2011) In neurofeedback studies, placebo effects could play a significant role in the observed behavioral changes. Real behavioral changes induced by the modulated brain activity could possibly be less than the changes induced by super-placebo effects.

Despite the necessity of the sham-control, many neurofeedback studies abandoned sham-controls because of ethical concerns. To avoid being derived from the Nuremberg Code and the Declaration of Helsinki, designs that withhold or deny the “the best proven diagnostic and therapeutic” treatment to any participant and were prohibited because it may lead to a deterioration of symptoms. (Vaque, 2001) Hence, sham-controlled neurofeedback studies can only be performed in healthy subjects or treatment-resistant subjects. (Jacek Rogala, 2016; Vaque, 2001)

### 4.4 Limitations

Several limitations exist in the present study. First, the training intensity is not high enough to engender long-lasting changes of iAPFs. Although the within-day increasing trends were exhibited in the NFT group, significant iAPF regresses emerged after 24 hours. Designs with more training sessions and intensities are required to further investigate the effectiveness and feasibility of the iAPF NFT in the clinical treatment of diseases related to low iAPFs, e.g. Alzheimer's diseases. Secondly, the sample size is not large enough, which does allow behavioral performance in n-back tests to be statistically analyzed by parametric methods or normalizer transformations. In addition, EEG data recorded during behavioral tests haven't been analyzed due to technical difficulty and incompleteness. Some temporal features could be regarded as indicators for evaluating behavioral performances. For example, event-related synchronization and desynchronization, i.e. ERS and ERD, of mental rotation tests had been reported to be related with mental rotations. (Klimesch et al., 2007)

# CHAPTER 5 CONCLUSION

In summary, our findings demonstrate that an intra-individually increased iAPFs, through neurofeedback training, may induce the enhancement of cognitive performances. Following detailed conclusions could be drawn:

a) EEG results indicated that iAPF at parietal and occipital regions can be up-regulated by haptic feedbacks in the eyes-closed condition and can achieve temporary changes in healthy adults via 15 mins training. It showed the possibility to use the iAPF as the training protocol for long-term NFT for cognitive enhancement.

b) The NFT group yielded significant promotion of the accuracy in mental rotation test and significant reduction of commission and omission errors in 3-back test in comparison with the sham group.

c) This study demonstrated intra-individually increased iAPFs accompanied by the enhancement of the cognition performance, which implied the evidence to determine the causality between the iAPF and cognition.

………

# REFERENCES


Amthauer, R. ,1970. “Intelligenz-Struktur-Test (I-S-T-70)” Göttingen, Germany: Hogrefe.

Angelakis E, Stathopoulou S, Frymiare J L, et al., 2007. “EEG neurofeedback: a brief overview and an example of peak alpha frequency training for cognitive enhancement in the elderly”. The Clinical Neuropsychologist, 2007, 21(1): 110-129.

Bauer, Robert, and Alireza Gharabaghi, 2015. "Estimating cognitive load during self-regulation of brain activity and neurofeedback with therapeutic brain-computer interfaces." Frontiers in behavioral neuroscience 9 (2015): 21.

Bazanova, O.M., 2012. “Comments for current interpretation EEG alpha activity: A review and analysis”. Journal of Behavioral and Brain Science, 2012.

Chalder, Trudie, et al.,1993 “Development of a fatigue scale.” Journal of psychosomatic research 37.2 (1993): 147-153.

Coben R, Evans JR., 2011 “Neurofeedback and neuromodulation techniques and applications”. London: Elsevier; 2011.

Escolano, C., Navarro-Gil, M., Garcia-Campayo, J., & Minguez, J. , 2014. “The effects of a single session of upper alpha neurofeedback for cognitive enhancement: a sham-controlled study”. Appl Psychophysiol Biofeedback, 39(3-4), 227-236

Foroughi C K, Monfort S S, Paczynski M, et al., 2016. “Placebo effects in cognitive training”. Proceedings of the National Academy of Sciences, 2016: 201601243.

Gharabaghi A, Kraus D, Leao M T, et al., 2014. “Coupling brain-machine interfaces with cortical stimulation for brain-state dependent stimulation: enhancing motor cortex excitability for neurorehabilitation”. Frontiers in human neuroscience, 2014, 8: 122.

Gittler,G.,2007.“Raumvorstellungsdiagnostikum: Adaptiver Dreidimensionaler Würfeltest (A3DW)”. Modeling, 23rd edition. Schuhfried GmbH.

Grandy T H, Werkle - Bergner M, Chicherio C, et al., 2013a “Peak individual alpha frequency qualifies as a stable neurophysiological trait marker in healthy younger and older adults”. Psychophysiology, 2013, 50(6): 570-582.

Grandy T H, Werkle-Bergner M, Chicherio C, et al., 2013b. “Individual alpha peak frequency is related to latent factors of general cognitive abilities” Neuroimage, 2013, 79: 10-18.

Hanslmayr S, Sauseng P, Doppelmayr M, et al., 2005. “Increasing individual upper alpha power by neurofeedback improves cognitive performance in human subjects”. Applied psychophysiology and biofeedback, 2005, 30(1): 1-10.

Hockey A, Geffen G., 2004. “The concurrent validity and test–retest reliability of a visuospatial working memory task”. Intelligence, 2004, 32(6): 591-605.

Jasper, H., 1958. “Report of the committee on methods of clinical examination in electroencephalography”. Electroencephalogr. Clin. Neurophysiol. 10:370–375.

Kasten F H, Herrmann C S., 2017. “Transcranial alternating current stimulation (tACS) enhances mental rotation performance during and after stimulation”. Frontiers in human neuroscience, 2017, 11.

Klimesch, W., 1996. “Memory processes, brain oscillations and EEG synchronization”. International Journal of Psychophysiology 24, 61–100.

Klimesch, W., 1999. "EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis." Brain research reviews 29.2 (1999): 169-195.

Klimesch, W., Sauseng, P., and Gerloff, C., 2003“Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency”. Eur. J. Neurosci. 17, 1129–1133

Klimesch, W., Sauseng, P., and Hanslmayr, S, 2006. “EEG alpha oscillations: the inhibition-timing hypothesis”. Brain Res. Rev. 53, 63–88. doi: 10.1016/j.brainresrev.2006.06.003

Klimesch, W.,1997. “EEG-alpha rhythms and memory processes”. International Journal of Psychophysiology, 26, 319–340.

La Vaque T J, Rossiter T., 2001. “The ethical use of placebo controls in clinical research: the Declaration of Helsinki”. Applied psychophysiology and biofeedback, 2001, 26(1): 23-37.

Martinez, Pablo, Hovagim Bakardjian, and Andrzej Cichocki, 2007. "Fully online multicommand brain-computer interface with visual neurofeedback using SSVEP paradigm." Computational intelligence and neuroscience 2007 (2007): 13-13.

Micoulaud-Franchi J A, Mcgonigal A, Lopez R, et al., 2015. “Electroencephalographic neurofeedback: Level of evidence in mental and brain disorders and suggestions for good clinical practice”. Neurophysiologie Clinique/Clinical Neurophysiology, 2015, 45(6): 423-433.

Müller K R, Tangermann M, Dornhege G, et al., 2008. “Machine learning for real-time single-trial EEG-analysis: from brain–computer interfacing to mental state monitoring”. Journal of neuroscience methods, 2008, 167(1): 82-90.

Nan W, Rodrigues J P, Ma J, et al., 2012. “Individual alpha neurofeedback training effect on short term memory”. International journal of psychophysiology, 2012, 86(1): 83-87.

Posthuma D, Neale M C, Boomsma D I, et al., 2001. “Are smarter brains running faster? Heritability of alpha peak frequency, IQ, and their interrelation.” Behavior genetics, 2001, 31(6): 567-579.

Rogala, J., Jurewicz, K., Paluch, K., Kublik, E., Cetnarskiand, R., Wróbel, A, 2016. “The Do’s and Don’ts of Neurofeedback Training: A Review of the Controlled Studies Using Healthy Adults”. Frontiers in Human Neuroscience, June 2016.

Rogel, Ainat, Jonathan Guez, Nir Getter, Eldad Keha, Tzlil Cohen, Tali Amor, and Doron Todder, 2015. "Transient Adverse Side Effects During Neurofeedback Training: A Randomized, Sham-Controlled, Double Blind Study." Applied psychophysiology and biofeedback (2015): 1-10.

Sitaram R, Ros T, Stoeckel L, et al., 2016 “Closed-loop brain training: the science of neurofeedback”. Nature Reviews Neuroscience, 2016.

Susanne M. Jaeggi , Martin Buschkuehl , Walter J. Perrig & Beat Meier, 2010. “The concurrent validity of the N-back task as a working memory measure”, Memory, 18:4.

Thibault R T, Lifshitz M, Raz A., 2017.“Neurofeedback or neuroplacebo?”. Brain: a journal of neurology, 2017, 140(4): 862-864.

Zoefel B, Huster R J, Herrmann C S, 2011. “Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance”. Neuroimage, 2011, 54(2): 1427-1431.

# PUBLICATIONS

Benzheng Li. (2015) "Effectiveness of flickering video clips as stimuli for SSVEP-based BCIs." TENCON 2015 IEEE Region 10 Conference.

Benzheng Li, Wenya Nan, Feng Wan, Sio Hang Pun, Mang I Vai, Agostinho Rosa. " Individual alpha peak frequency neurofeedback training improves cognition: a sham-controlled study in healthy adults" submitted to Frontiers in Human Neuroscience.