Effects of Alpha and Gamma Neurofeedback Training on Schizophrenics' Working Memory Performance

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1. Abstract

Neurofeedback (an operant conditioning methodology that allows subjects to learn self-control over brain oscillations) has been used to alter abnormal brain activities in dysfunctional brains. Schizophrenia (SCZ) is associated with abnormal brain rhythms, both during rest and working memory (WM) processing. Studies have shown that abnormal alpha brain rhythms (8-12 Hz) appear to interfere with a subject's state of resting wakefulness and ability to inhibit task-irrelevant information, while abnormal gamma rhythms (35-45 Hz) impact a subject's maintenance of working memory (WM). These abnormalities exist in SCZ, with association to their deficits in WM. In this project, we examined EEG data from SCZ subjects who were trained to increase both gamma and alpha coherence (i.e., degree of similarity in amplitude at two electrode sites) over frontal brain regions using neurofeedback. We assessed the effects of an interaction between gamma and alpha NFB on working memory (WM) and brain activities during rest and WM processing in SCZ, and characterize any temporal interactions between these rhythms that affects training. We found that a combination of training alpha and gamma coherence did improve WM in SCZ, and increased alpha and gamma power during rest,

but not WM processing. This occurred only when the training on gamma coherence was given first.

2. Introduction

Schizophrenia (SCZ) is a disorder typically associated with abnormal brain rhythms during rest as well as working memory (WM) processing. Compared to neurotypical subjects, a number of brain EEG rhythms show abnormalities in this population. Moran and Hong (2011) showed that SCZ patients exhibit reduced power (i.e., square of the amplitude) and abnormal coherence (i.e., degree of similarity in amplitude at two electrode sites) in alpha rhythms (8-12 Hz) while the brain is idling (i.e., at rest), as well as when paying sustained attention. The gamma rhythm (35-45 Hz) in working memory (WM) condition is similarly abnormal in this population in that it shows decreased power and synchronization.

The EEG alpha rhythm is a prominent brain oscillation in healthy humans that is present when the brain is in a state of resting wakefulness (Pfurtscheller, 1996). Increased power in alpha rhythms is seen at prefrontal sites when the brain is involved with a WM task since the increased alpha amplitude is assumed to be a reflection of increased biophysical inhibition in the processing of task-irrelevant stimuli (Sauseng et al., 2005). Besides the alpha rhythm, gamma oscillation increases during a WM task presumably to serve the function of maintaining WM (Howard et al., 2003). Growing evidence has indicated that high-frequency rhythms, such as gamma, and low-frequency ones, such as alpha, are "coupled," i.e., associated with each other in terms of cognitive functions. Therefore, one potential explanation of the WM process is that

gamma and alpha brain oscillations work together to maintain WM. In neurotypical population, alpha and gamma brain oscillations at WM processing have high power.

Due to the evidence that schizophrenics have abnormally low alpha and gamma activity during WM processes, we examined whether enhancing alpha and gamma coherence could improve WM performance. Coherence is the degree of similarity in amplitude at two electrode sites. The coherence we enhanced is across sites F3 and F4, located at the left and the right frontal lobe. Since coherence represents the connectivity across the brain, we decided to train on coherence at F3 and F4 so that the effect can be spread across both left and right frontal lobes. Subjects received neurofeedback (NFB) training to enhance the coherence of either gamma or alpha oscillations twice a week for 4 weeks in a crossover design. That is, some subjects received gamma training first and then switch to alpha training, while others began with alpha and then switched to gamma training. NFB allows subjects to learn self-control over brain oscillations by using visual cues that act as metaphors for the level of activity occurring in real time. NFB has been used to train gamma coherence in the frontal lobe and improved WM in healthy (HC) populations (Keizer et al., 2010). We hope that this effect from healthy populations can be replicated in SCZ subjects, with the addition of NFB on alpha coherence. The question we were asking was: does a combination of training on alpha and gamma coherence increase schizophrenics' overall alpha and gamma power, and does this improve their WM performance? We assessed the effects of gamma and alpha training on WM in SCZ, and their temporal interactions (i.e., does it matter if one frequency is trained first?). The power and frontal asymmetry (i.e., the distribution of brain activities across left and right frontal lobes) of alpha

and gamma rhythms were assessed before and after trainings and then analyzed to examine changes.

We hypothesize that: 1) a combination of training on alpha and gamma coherence will increase schizophrenics' alpha and gamma power at both resting state and WM state, and 2) that these changes in electrophysiology will improve schizophrenics' WM performance. Secondarily, we hypothesize that the increase in coherence/power will be evenly distributed across left and right frontal lobes.

3. Methods

3.1 Participants

This is a secondary data analysis project, using data collected from a previous study of gamma neurofeedback training on a SCZ population. Thirty neurotypical participants and fourteen SCZ participants were recruited for the original study. Data from eight neurotypicals were discarded since they had a clinical diagnosis of other psychiatric disorders. Six SCZ participants' data were discarded due to incomplete training, where subjects dropped out and diagnosis of other types of psychiatric disorders occurred, besides SCZ. Thus, twenty-two neurotypical subjects out of thirty and eight SCZ subjects out of fourteen were used for data analysis. Four SCZ subjects (SCZ Group1) had four weeks of NFB training on gamma frequency (G-NFB) first and then another four weeks of NFB trainings on alpha frequency (A-NFB). The other four SCZ subjects (SCZ Group2) had four weeks of A-NFB first and another four weeks on G-NFB.

3.2 Electrophysiological Recording

EEG was recorded from 19 electrode sites on the scalp (F1, F2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, O1, O2) and referenced to linked ears using the Cognionics EEG dry-electrode headset and recording software. The recording equipment and software were provided by Cognionics. The data were collected at a sampling rate of 256 Hz and filtered by a 120 Hz low pass filter. The EEG data collected were cleaned using EEGLAB.

3.3 Assessment Materials

Participants were assessed in a variety of ways (resting state, during a WM task, and using a neuropsychological assessment battery).

3.3.1 Resting State

Resting state EEG was recorded from all subjects. Throughout the resting state session, subjects were asked to close their eyes (eyes closed (EC) condition) for five minutes while sitting and minimizing body or head movements. After a minute break, subjects were asked to keep their eyes open (EO) for five minutes while remaining still.

3.3.2 WM Task: N-back Test

EEG was also recorded from all the subjects during an n-back test. N-back is a task that quantifies WM performance (Jaeggi, 2008). When the visual or auditory stimuli match the

stimuli presented ‘n’ times before, the subject is required to respond. In this study, we used a two-back test paradigm to measure the subjects’ WM performance (Figure 1).

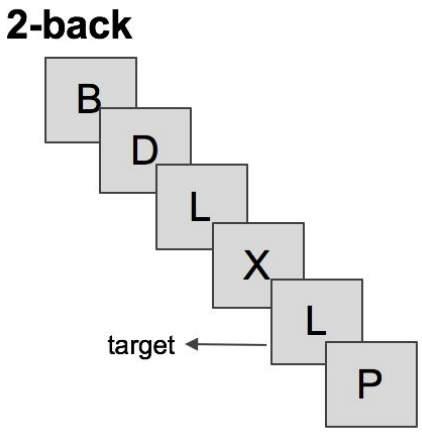


Figure 1. 2-back Task Paradigm. The individual letters appeared on the screen in a random order. When one letter matches the letter presented before the previous card, that letter is a target. Subjects were required to respond to the target.

3.3.3 Neuropsychological Assessment: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Update

RBANS Update test assesses an individual’s neuropsychological status in aspects of attention, language, visuospatial/constructional abilities, and immediate and delayed memory. All subjects in this study received RBANS assessment.

3.3.4 Neurofeedback (NFB) Training

Only SCZ subjects received NFB training, a 45-minute training session twice a week. A video of a game was played to the subjects for 45 minutes. Two electrodes were placed on their scalp to transmit their real-time brainwaves data. During the gamma (or alpha) NFB training, the subject was required to keep the real-time coherence of gamma (or alpha) frequency above a

predetermined threshold in order to keep the video playing and hearing pleasant music. If the real-time value fell below the threshold, the video and the music would stop playing.

4. Procedure

Data were collected at three time points: t=0 (the pre-training measure), t=1 (SCZ subjects finished the NFB training on one frequency band twice a week for 4 weeks), and t=2 (SCZ subjects finished the NFB training on the second frequency band twice a week for 4 weeks). At t=0, the EEG data, the results of the two-back test, and the resulting assessment of RBANS were collected from both the neurotypical and SCZ subjects. At t=1, when half of the SCZ subjects completed G-NFB and the other half finished A-NFB, the EEG data, the result of the two-back test, and the resulting assessment of RBANS were collected from all the SCZ subjects. Same procedure applied to the t=2 time point (Figure 2).

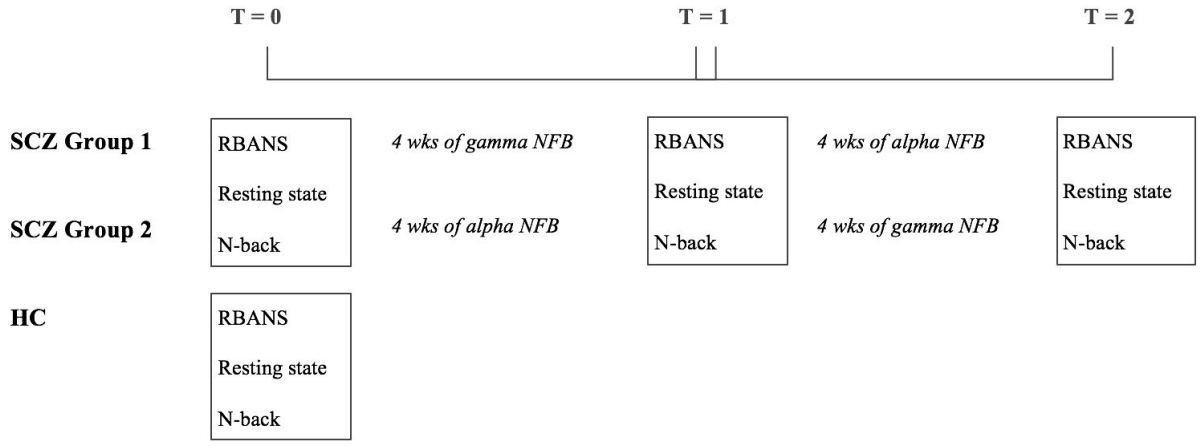


Figure 2. The experimental design. Two groups of SCZ subjects had G-NFB and A-NFB in a crossover design and received three assessments (RBANS, Resting State, two-back WM test) at t=0, t=1, and t=2. Neurotypical subjects only received assessment at t=0 and did not receive any NFB training.

5. Data Analysis

The EEG data was first processed through EEGLAB, where it was filtered using a bandpass ranging from 0.5 to 60 Hz and re-referenced to the average channel value. Independent Component Analysis (ICA) was applied to remove noisy components. All the other artifacts were visually detected and removed. The EEG data was then decomposed into alpha (8-12 Hz) and gamma (35-45 Hz) frequency bands using MATLAB. The absolute power of each frequency band at each of the following frontal electrode site, F7, F3, Fz, F4, and F8 was calculated through MATLAB using specto function embedded in EEGLAB. The relative power was then calculated by:

$$relative\ power\ = \frac{absolute\ power\ of\ one\ frequency\ band\ at\ each\ site}{absolute\ power\ of\ all\ frequencies\ at\ each\ site}\ .$$

The asymmetry index of alpha and gamma frequency band was calculated by:

$$index\ =\ log\frac{absolute\ power\ at\ F4}{absolute\ power\ at\ F3}$$

where F4 and F3 are two electrode sites each located on the right and the left frontal lobe. The RBANS results, the two-back WM test scores, and the alpha power, gamma power, alpha asymmetry index, and gamma asymmetry index at both resting state and WM state were compared across three subjects groups and across t=0, t=1, and t=2. Due to the small size of subject population, all the data were analyzed by using exploratory data analysis approach without statistical measurements.

6. Results

6.1 RBANS

SCZ Group1 had a gradually increasing trend on the score of immediate memory in RBANS, from t=0 to t=1 to t=2 (Figure 3). It indicates that schizophrenia subjects, who had a combination of training in the sequence of G-NFB first and A-NFB second, showed an improved immediate memory at t=2 versus t=0. This gradually increasing trend was missing in SCZ Group2 subjects who received A-NFB training prior to G-NFB. Both SCZ groups did not show improvements on the total score of RBANS.

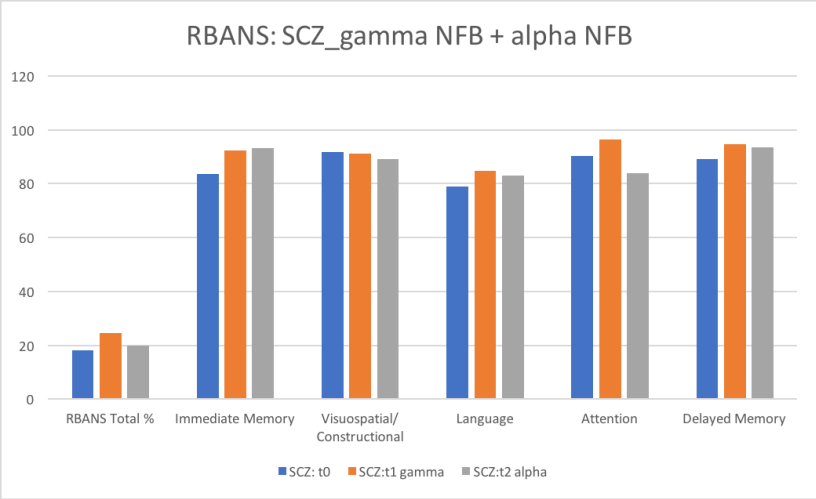


Figure 3. Immediate memory in SCZ Group1 across t=0, t=1, and t=2.

6.2 Two-Back WM Test

SCZ Group1 had a gradual increase on 2-back scores from t=0 to t=1 to t=2 (Figure 4). This ascending trend was not seen in SCZ Group2. It suggests that the combination of A-NFB and G-NFB did improve schizophrenics' WM performance, but only when G-NFB was provided first.

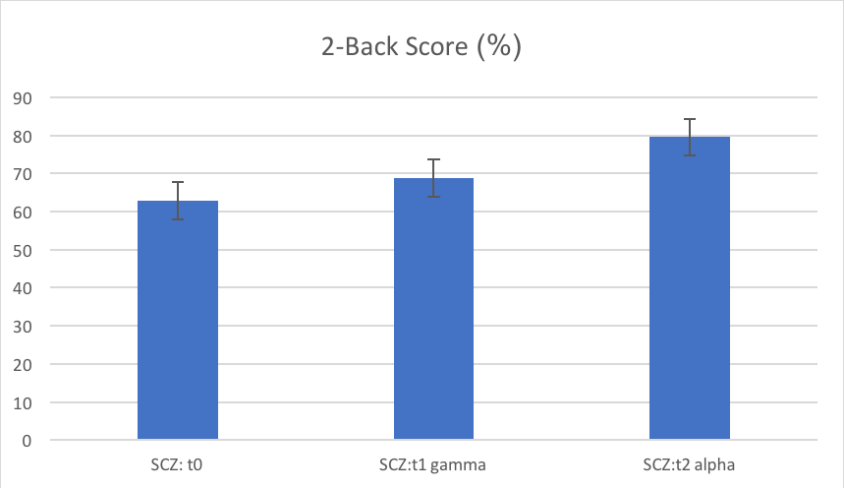


Figure 4. Two-back scores in SCZ Group1 across t=0, t=1, and t=2.

6.3 EEG Data

6.3.1 Power at Resting State

In the EC condition, SCZ patients at t=0 had a lower alpha power at electrode sites F3, Fz, F4, and F8, and a lower gamma power at electrode sites F3, Fz, and F4 (Figure 8) compared to HC. At t=2, SCZ Group1 showed an increased alpha power on all the electrode sites analyzed, and an increased gamma power on electrode sites F7, F3, Fz, and F4 (Figure 9). These two increasing trends were missing in the SCZ Group 2. This indicates that a combination of training did increase alpha and gamma power for SCZs at their resting state as was expected, but only in the sequence in which G-NFB was provided first followed by A-NFB. In the EO condition, SCZ patients had a lower gamma power at all frontal electrode sites measured, and a lower alpha power at electrode sites F3 and Fz (Figure 10) versus HC. At t=2, SCZ Group1 showed an increased gamma power at electrode sites F7, F3, and Fz, and an increased alpha power at electrode sites F3 and Fz (Figure 11). No changes were detected in SCZ Group2 after training. It implies that SCZ subjects' gamma and alpha abnormalities under EO condition were affected to

some extents through NFB training, but again only in the sequence in which G-NFB is provided first followed by A-NFB.

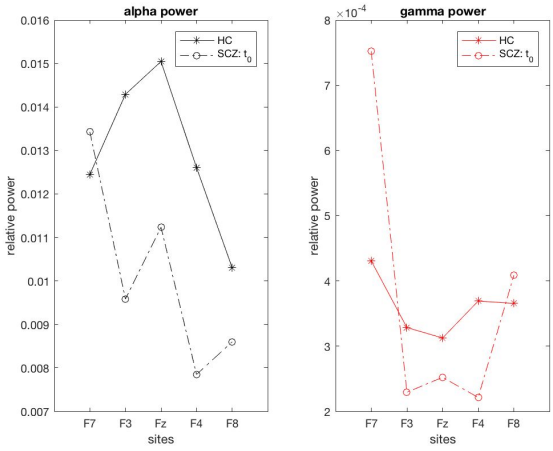


Figure 8. Alpha and gamma power at resting state (EC) in all SCZ subjects at t=0 and HC subjects.

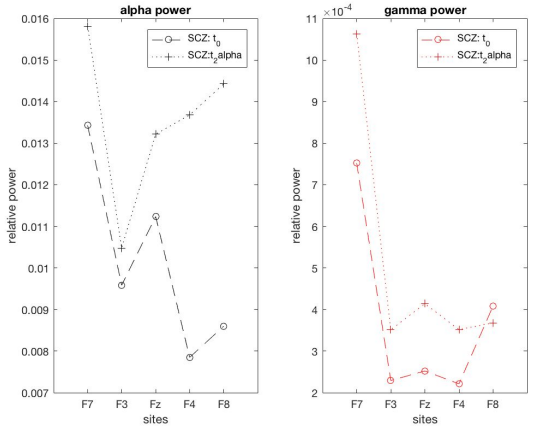


Figure 9. Alpha and gamma power at resting state (EC) in SCZ Group1 at t=0 and t=2. Subjects in SCZ Group1 had G-NFB for four weeks first and then A-NFB for another four weeks.

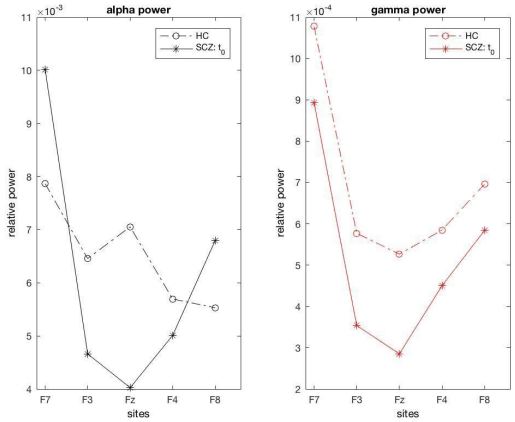


Figure 10. Alpha and gamma power at resting state (EO) in all SCZ subjects at t=0 and HC subjects.

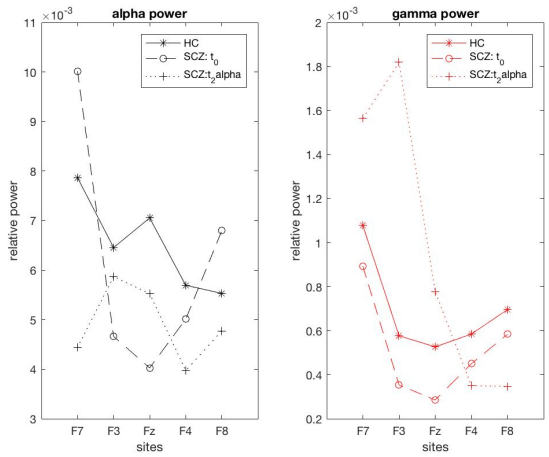


Figure 11. Alpha and gamma power at resting state (EO) in all HC subjects, and SCZ Group1 at t=0 and t=2. Subjects in SCZ Group1 had G-NFB for four weeks first and then A-NFB for another four weeks.

6.3.2 Power during WM task

We found that compared to HC, SCZ patients at t=0 had lower alpha and gamma power at electrode sites F3 and Fz (Figure 5). At t=2, SCZ Group1 showed reduced alpha power at all the frontal electrode sites analyzed, and reduced gamma power at all the electrode sites except for F8 (Figure 6). SCZ Group2 at t=2 showed increased alpha power at electrode sites F7, Fz, and F8, and increased gamma power at electrode sites Fz, F4, and F8 (Figure 6). These results indicate that a combination of training increased alpha and gamma power during the WM task in SCZ when A-NFB was given first, and decreased when G-NFB was given first. However, it was SCZ Group1, who had G-NFB first, that had improvement on WM performance at t=2 (Figure 4). This indicates SCZ's improved WM performance was associated with a decrease in their relatively low alpha and gamma power, which was opposite to what we expected.

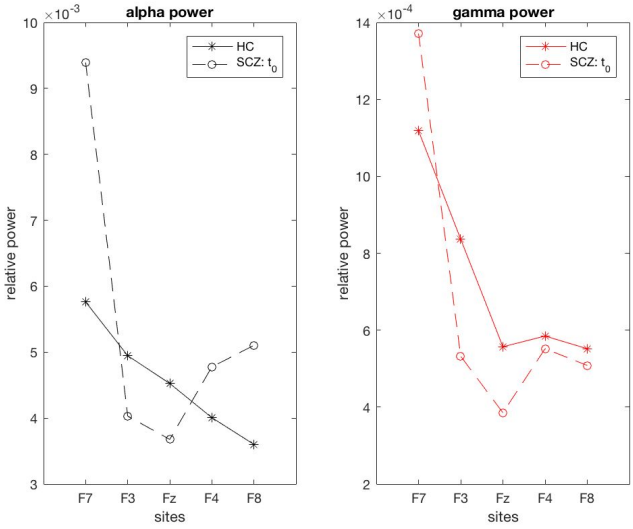


Figure 5. Alpha and gamma power at WM state in all SCZ subjects at t=0 and HC.

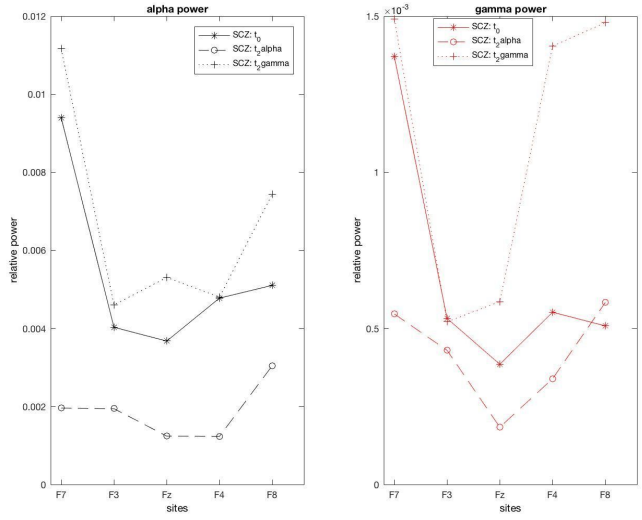


Figure 6. Alpha and gamma power at WM state in all SCZ subjects at t=0 and t=2.

6.3.3 Asymmetry during the WM Task

Similar to HC, SCZ subjects at t=0 had alpha asymmetry index and gamma asymmetry index within the range from -0.1 to +0.1, which indicates both neurotypical subjects and schizophrenic patients had evenly distributed alpha and gamma activities across left and right

frontal lobes. At t=2, SCZ Group2 exhibited an increased gamma asymmetry index over +0.1, meaning their distribution of gamma activity over the frontal lobe was right-shifted. SCZ Group1 showed decreased alpha and gamma asymmetry index below -0.1, which indicates their distributions of alpha and gamma activity were more left-shifted over the frontal lobe (Figure 7). Since SCZ Group1 showed improvement on their WM, we interpret this to mean that improved WM is associated with a left-shifted distribution of alpha and gamma activity over the frontal lobe, with an overall decrease in alpha and gamma power.

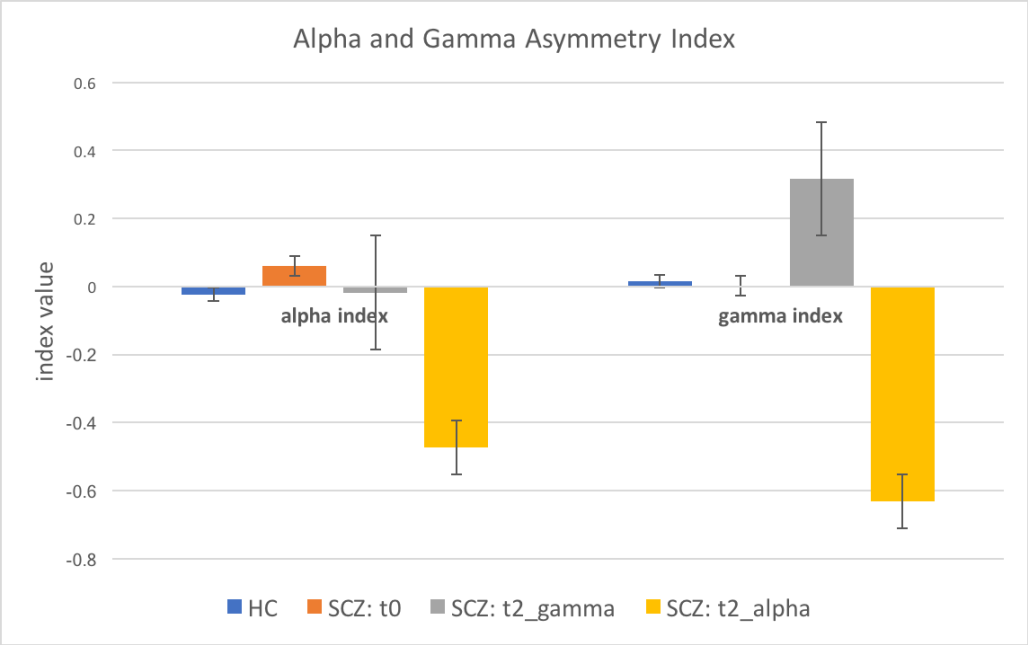


Figure 7. Alpha and gamma asymmetry at WM state across HC subjects and all SCZ subjects at t=0 and t=2.

6.3.4 Asymmetry during the Resting State

In EC and EO conditions, both SCZ patients and HCs at t=0 had alpha and gamma asymmetry index within the range from -0.1 to +0.1 (Figure 12 and Figure 13). This suggests both had evenly distributed alpha and gamma activities across left and right frontal lobes while they were resting with their eyes closed and opened. In EC condition, at t=2, increased alpha and gamma asymmetry indexes above +0.1 were produced in SCZ Group1, indicating that subjects who had G-NFB prior to A-NFB had more alpha and gamma power on the right frontal lobe following trainings. SCZ Group2 had a lower alpha asymmetry index below -0.1(Figure 12), which indicates that subjects who had A-NFB prior to G-NFB had more alpha power on the left frontal lobe following training. No gamma asymmetry change was seen in SCZ Group2. In EO condition, at t=2, SCZ Group1 had an increased alpha asymmetry index above +0.1 and a reduced gamma asymmetry index below -0.1 (Figure 13). This means SCZ patients who had G-NFB prior to A-NFB had more alpha power on the right frontal lobe versus left, and more gamma activity on the left frontal lobe compared to the right following training. Neither alpha asymmetry nor gamma asymmetry changed in SCZ Group1 and Group2 after training.

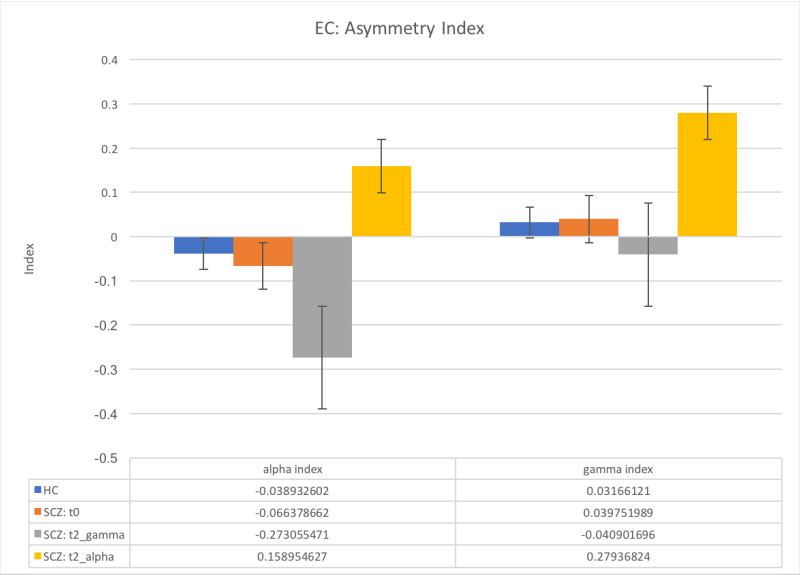
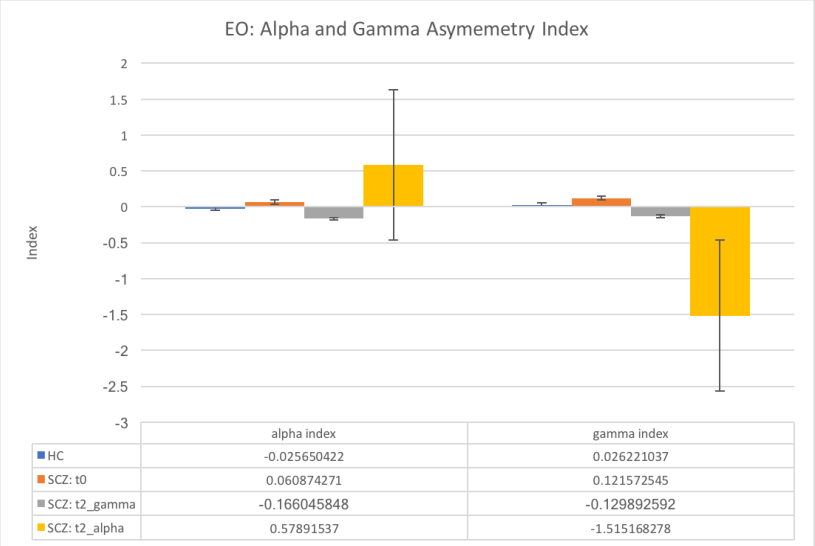


Figure 12. Alpha and gamma asymmetry at resting state (EC) in all HC subjects and all SCZ subjects at t=0 and t=2.



	alpha index	gamma index
HC	-0.025650422	0.026221037
SCZ: t0	0.060874271	0.121572545
SCZ: t2_gamma	-0.166045848	-0.129892592
SCZ: t2_alpha	0.57891537	-1.515168278

Figure 13. Alpha and gamma asymmetry at resting state (EO) in all HC subjects and all SCZ subjects at t=0 and t=2.

7. Discussion

This study examined whether a combination of training of alpha and gamma coherence would increase schizophrenics' abnormally low alpha and gamma power in the frontal lobe during the WM process, and whether this would improve the patients' WM performance. We found that a specific combination of training did improve schizophrenics' WM performance, but only when the G-NFB was provided first. This specific sequence of NFB training did increase schizophrenics' alpha and gamma power during resting state, but decreased their already abnormally low alpha and gamma power during the WM process. Furthermore, under the WM condition, alpha and gamma activity from SCZ patients across left and right frontal lobes transitioned from an fairly symmetrical distribution to a left-dominant distribution after training in which G-NFB came first and A-NFB followed.

These results suggests that NFB is a technique that can modify SCZ patients' WM and brain activity, but that the patients' improvement on WM is not essentially associated with the increase of their alpha and gamma power during the WM task. Although there is no statistical testing in this study, there is the possibility that SCZ patients' improvement on WM is associated with more alpha and gamma activity over the left frontal lobe.

A potential reason why alpha and gamma power in the WM task responded in a different manner than we expected is that we trained SCZ subjects to increase their alpha and/or gamma coherence across F3 and F4 sites by using NFB. However, we analyzed the subjects' alpha and gamma power, which are values on each individual electrode site. In future analysis, we can measure coherence between F3 and F4 electrode site before and after training, in order to see if these values are improved after the trainings, which would give us more information about the effects of NFB on alternating brain activities.

SCZ subjects in our study showed improvement on their WM performance with a decrease in gamma power, which was opposite to previous study in which WM performance was positively correlated with the value of gamma power (Howard et al., 2003). One potential explanation is that the WM task used in the Howard et al.'s experiment measures the working memory load while the n-back test we used measures one's WM performance. The difference between these two tests can potentially explain why there was a dissociation between WM and gamma power happened in our study.

Another question is why the NFB training affected SCZ subjects' brain activity at resting state as expected, but did not affect their brain activity during the WM task? The abnormally low alpha power at resting state in SCZ patients has been shown by several studies, so that our

hypothesis that NFBs would increase SCZ subjects' alpha power at resting state had a strong rational basis. However, the explanation of WM processing (high alpha and gamma power are present during the WM processing) which our hypothesis based on is one of the many competing explanations of WM. Erickson et al. (2017) found that SCZ's deficits in WM is associated with their failure of alpha suppression, which means SCZ's abnormally high alpha power is associated with their deficits in WM. Because there are mixed findings on SCZ's alpha brain oscillation at WM processing, our hypothesis that increased alpha and gamma power at WM would lead to an improvement on WM was based on a weaker basis. This is why NFB had different effects on SCZ's brain activities at resting state and WM processing.

In summary, we did use NFB training to improve SCZ patients' WM performance and to increase their alpha and gamma power at the resting state, but we did not alter their abnormal brain activities during a WM task as we expected. Additionally, we did find that the effective combination of training lies in the temporal sequence of G-NFB first followed by A-NFB. This study examined how alpha and gamma rhythms interact in SCZ with the intent to improve the brain's ability to modulate activities related to improved WM, and provides insights for improving NFB training for this disorder.

8. References

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