Psilocybin-Assisted Neurofeedback: A Multimodal Approach to Improving Executive Functions

Raquel Castillo Bihler

S3971813

Department of Psychology, University of Groningen

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Supervisor: Dr. Stefanie Enriquez-Geppert

Second evaluator: Anika Poppe

In collaboration with: Fiachra O'Higgins

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Abstract

Executive functions are thought to be fundamental for success in a myriad of domains. However, since they are needed in difficult situations implementing these higher cognitive functions require increased amounts of cognitive power. Specifically for executive functions, frontoparietal theta band oscillations are suggested to be an underlying substrate of these cognitive control processes. Disruptions of frontoparietal theta oscillations has been linked to neuropsychological disorders, hence why upregulation of theta oscillations is important for several reasons. In this study, we are specifically interested in upregulation of theta amplitude and through its mechanisms are thought to achieve improved cognitive functions. Neurofeedback provides a promising technique to promote neuroplastic changes which help to improve cognitive impairments. In addition to neurofeedback, which acts on a top-down mechanism, psilocybin, a serotonergic psychedelic, acts upon neuroplasticity mechanisms from a bottom-up perspective. Together they form a new approach to enhance cognitive function. This study employed a naturalistic paradigm where participants took a psilocybin micro-dose and were given three neurofeedback training session. This study investigated if improvements in an executive function test-battery assessing conflict monitoring, set-shifting, response inhibition, and working memory updating after the psilocybin-assisted neurofeedback intervention could be observed. This study was to our knowledge the first to examine this novel approach and therefore paves the way for future research as a rehabilitation tool for clinical practice.

Keywords: executive functions, neurofeedback, psilocybin, plasticity, (frontal midline) theta oscillations

Psilocybin-Assisted Neurofeedback: A Multimodal Approach to Improving Executive Functions

Successful everyday life functioning is linked to the implementation of higher cognitive processes, specifically executive functions (EF, Friedman & Miyake, 2017). EFs are an umbrella term for several different top-down mental processes which are needed when automatic routines no longer apply, hence in novel or difficult situations (Diamond, 2013), yet implementing EFs is effortful and requires increased cognitive power. Although EFs encompass a broad range of interrelated terms of higher cognitive functions, there are four main processes that are of particular importance. These are: set-shifting, working memory updating, conflict monitoring, and response inhibition, (Miyake et al., 2000). Further, these control processes have been linked to theta band oscillations, especially those generated in the frontal medial neocortical structures, also called frontal midline (fm) theta. These oscillations have been hypothesized to be an underlying substrate of EFs and may help in the modulation of several cognitive control processes required in daily life. Some forms of cognitive training may improve fm-theta self-regulation which has been shown to predict successful behavioral performance (Dashbozorgi et al., 2021). Neurofeedback is such a tool where the participant tries to alter or control their brain function by implementing certain cognitive strategies and does so by means of live feedback of their brain activity. This method can be achieved with non-invasive neuroimaging tools, such as electroencephalography (EEG) and may provide an effective tool for improving cognitive impairments across various psychological disorders. However, the translation of desired clinical or behavioral changes are often unclear and the exact mechanisms of how the neuroplastic changes are achieved are still unknown (Hampson et al., 2020). This study aims to shed some light on the mechanisms towards plasticity in neurofeedback training.

In general, EF tasks can be divided into proactive and reactive control processes (Braver, 2012). Proactive control describes top-down processes that facilitate execution of cognitively demanding tasks and achievement of goal-directed behavior before the event has happened. For this, set-shifting and working memory updating can be considered proactive processes (Eschmann & Mecklinger, 2022). In contrast, reactive control is regarded as a correction process which allows for inhibition of task irrelevant behaviors in a conflicting event. Tasks measuring conflict monitoring and response inhibition are considered reactive control processes (Eschmann & Mecklinger, 2022). Central to this, are brain networks and neural oscillations that are involved in the modulation of higher cognitive processes, including both reactive and proactive control. In general, EFs rely on and are supported by several brain areas which form the fronto-parietal network (FPN) (Baddeley, 1998; Osaka et al., 2004). This network encompasses among other things, the midcingulate cortex (MCC), the dorsolateral prefrontal cortex (DLPFC), the prefrontal cortex (PFC) as well as subcortical structures such as the thalamus (Enriquez-Geppert et al., 2014). Together they form a complex superordinate network which have been found to be modulated by EF tasks. Especially, for complex cognitive functions, there are several brain regions overlying the medial prefrontal cortex (mPFC) that elicit synchronized oscillations when engaging in EF tasks. These synchronizations may occur within one neural network but also between different networks, which enables that these regions communicate with each other (Ward, 2003). Higher cognitive functions are thought to specifically rely heavily on one important neural oscillation: theta bands, which occur at the rate of 4-8Hz (Herweg et al., 2020). Theta oscillations are generated in the MCC during engagement of cognitive control and for that reason they are thought to be indicative of higher cognitive functions. In healthy individuals, the FPN has been found to execute complex goal-directed behavior and increases in fm-theta

amplitude when engaging in effortful tasks have been observed (Eisma et al., 2021). Therefore, fm-theta oscillations are of particular interest.

Generally, upregulation of fm-theta oscillations can be observed during execution of EF tasks. Thus, regulation of fm-theta may contribute to augmented cognitive function and improved cognitive reserve (Reiner et al., 2014). Regulation of band oscillations can be achieved through neurofeedback, which utilizes an active technique in terms of task engagement where the participant receives live feedback of their brain waves. It has been found to achieve long-term retention in upregulating brain activity and is therefore thought to promote enhanced plasticity (Sitaram et al., 2017). Despite the evidence that neurofeedback shows improvement on several cognitive as well as behavioral domains, it did not show transfer to all cognitive tasks. Studies have suggested that neurofeedback outcome is strongly mediated by psychosocial factors as well as specific neurophysiological signals (Wood & Kober, 2018; Ros et al., 2020). For that reason, predicting learning outcomes may be of particular interest. Specifically, the results suggest that proactive but not reactive control processes are able to benefit from fm-theta upregulation (Enriquez-Geppert et al., 2014; Eschmann & Mecklinger, 2022). Though, it has been suggested that multimodal treatment that targets several domains is more successful in modifying behavior than just neurofeedback alone (Garcia Pimenta et al., 2021). This is because the combination of several treatment modalities provides a broader spectrum of targeting different dysfunctional structures, and by doing so is thought to have an additive and/or synergistic effect. For neurofeedback training, studies have found network reorganization which suggests a top-down mechanism (Koush et al., 2015). Hence, combining treatments that could induce plasticity changes from a bottom-up level could facilitate the adaptation from a molecular perspective. One way this can be achieved is through serotonergic psychedelics.

There are many classes of psychedelics, but serotonergic psychedelics are considered a potent serotonin (5-Hydroxytryptamin) 2A receptor (5HT2A) agonist, and therefore facilitates the transmission of serotonin in the brain. Psilocybin is a serotonergic psychedelic that comes in form of mushrooms or truffles and is a prodrug which is transformed into its active metabolite psilocin, which has the actual hallucinogenic component. Psilocybin functions through arousal of pyramidal cells in the PFC and this excitation increases brain-derived neurotropic factor (BDNF), which is involved in neuroplastic mechanisms (Vollenweider & Kometer, 2010). Specifically, studies suggest that serotonergic psychedelics induce BDNF in the cortex but not in the hippocampus, which has been shown to negatively impact memory mechanisms and could therefore interfere with EFs needed in novel tasks (Healy, 2021). In addition, serotonergic psychedelics, such as psilocybin, are able to cross the blood-brain barrier more easily which makes it a convenient drug to use compared to other drugs that have more difficulty targeting structures in the brain (Kozlowska et al., 2020). It is important to note that these results have all been found on a macro-dose paradigm. For that reason, psychedelics are increasingly being recognized to offer potential treatment for neuropsychiatric and neurodegenerative disorders due to its bottom-up effects in synaptic plasticity (Shao et al., 2021). Recently, micro-dosing psychedelics has yielded interest in its promising effects for increased psychological functioning, such as alleviating depressive symptoms and improving mood (Kuypers, 2020; Rootman et al., 2022). Micro-dose practices involve administration of very small doses of the hallucinogenic agent, which do not alter the state of mind or regular functioning (i.e. at a subperceptual level). Thus, combining both neurofeedback and psilocybin yields an interesting multimodal approach to target neuropsychiatric disorders in order to modulate brain activity. This study aims to use the increase in plasticity to boost efficacy of the neurofeedback training and hence improve EFs.

In this study we specifically aim to investigate EFs and fm-theta upregulation. It is hypothesized that (1) participants who received the intervention (psilocybin assisted neurofeedback) will improve at upregulating their theta amplitude and will therefore show an increase in task performance on the EF test battery compared to those that did not receive the intervention. Since previous studies have found that upregulation of fm-theta during neurofeedback was only successful at improving proactive tasks, we specifically assume that set-shifting, and working memory updating will improve. However, since psilocybin is able to target broad areas, it may be assumed that this intervention will benefit tasks assessing conflict monitoring and response inhibition as well. Further, we will examine whether baseline measures of individual fm-theta amplitude are predictive of success for the EF tasks. It is hypothesized that (2) the baseline theta amplitude before neurofeedback training will be indicative of better performance on the proactive tasks.

Methods

Participants

18 healthy participants aged between 21-37 participated in this study (10 male, 8 female). They were semi-randomly allotted into two groups, the experimental group (N = 10) and a control group. Participants were sampled from a micro-dosing workshop conducted by the Dutch Microdosing Institute, to provide familiarity with psilocybin and ensure safety. Before the experiment, all participants gave their consent for the study and were given participant information according to the Ethics Committee of the Behavioral and Social Sciences from the University of Groningen (PSY-2122-S-0220). The study was in accordance with the declaration of Helsinki. The control group was not given the full information about the neurofeedback procedure and therefore were deceived from the actual nature of the study. This group was debriefed after the end of the experiment. No monetary compensation was

given to the participants; however the micro-doses were kindly sponsored by the Dutch Microdosing Institute for participants of this study.

Structure of Study

Truffles & Truffle Dosing

Participants received 12 fresh Psilocybe Mexicana (12x1g) truffles via the Dutch Microdosing Institute. Previous studies have estimated the dosage of psilocybin and psilocin contained in 1g of dehydrated truffles to be on average 1.14mg (Prochazkova et al., 2021). In order to find the appropriate individual micro-dose, participants first had an adjustment period. During this period, participants were advised to experiment with three varying dosages (between 0.5-2g) until they reached their preferred dose. More specifically, they were instructed to take a subperceptual dose of the hallucinogenic agent, which should not alter their regular functioning. During the experimental period, participants always self-administered two hours before coming into the neurofeedback session.

EF Assessment

Participants conducted the EF assessment remotely via the software OpenSesame (Mathôt et al., 2012) and the tests were hosted online via Jatos (MindProbe, European Society for Cognitive Psychology). Online group meetings were hosted on Zoom and questionnaires, which were administered before the web-based test battery, were implemented through the Qualtrics software.

Exclusion criteria

The exclusion criteria consisted of (1) participants had a history of psychotic mental disorders, in particular schizophrenia, (2) they had a family history of psychotic mental disorders, in particular schizophrenia, and (3) they were colorblind.

Procedure

The structure of the study is as follows: Participants attended the micro-dosing workshop and were then semi-randomly allocated into either the neurofeedback group (NFG) or the passive control group (PCG). Both groups were first measured on their cognitive functions with an EF test-battery. In this study, the micro-dosing protocol of the Microdosing Institute was used which instructed their users to take a micro-dose every second day (i.e. Tuesday, Thursday, Saturday, Monday, Wednesday, and Friday). As stated above, the first week (first three doses) served as the adjustment period for participants to regulate their preferred micro-dose. The second week consisted of three neurofeedback sessions on Monday, Wednesday, and Friday, where participants were instructed to take the last three micro-doses two hours before coming into the lab to receive their neurofeedback session. Following the pre-assessment only the NFG started micro-dosing and receiving their intervention. After two weeks since the pre-measurement, both groups completed the post measurement which was the same test-battery assessing EFs, completing the study for the NFG (Figure 1). After the second cognitive assessment, the PCG were instructed to follow the same micro-dose protocol from the Microdosing Institute, with first an adjustment period and then a stable micro-dose. After the two weeks of micro-dosing, participants in the PCG were given a third measurement, which was a sham assessment as did not collect any valuable data. This was done to give the illusion that something of importance was measured after they took the micro-dose. After completion, the participants were debriefed and received information of the true nature of the study.

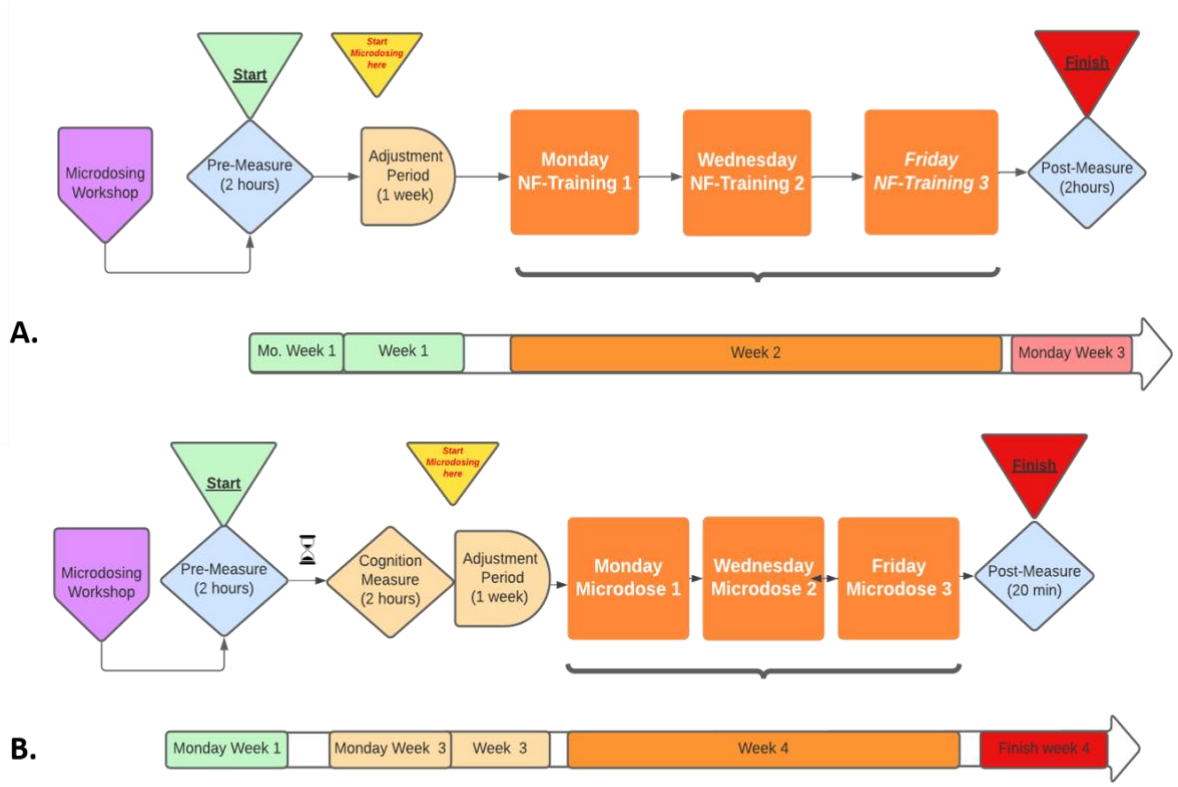

Figure 1: Overview of the study design. (**A.**) Participants in NFG underwent the first cognitive assessment (pre-measure) followed by 1 week of adjustment period of micro-dosing. Afterwards the intervention followed (psilocybin assisted neurofeedback) and then was finished with the second cognitive assessment (post-measure). (**B.**) Participants in PCG underwent the first cognitive assessment (pre-measure) and while the NFG had the intervention, this group waited until after completion of the second cognitive assessment (post-assessment) to start micro-dosing. Afterwards, this was followed by 1 week of adjustment period of micro-dosing and then regular micro-dosing after which a sham measure (third assessment) was given to them.

Tasks and Stimuli – Executive Function Assessment

The test battery consisted of the four EF core components assessing conflict monitoring, response inhibition, set-shifting, and working memory updating. While conflict monitoring and response inhibition are considered reactive cognitive control tasks, the tasks

assessing set-shifting and working memory updating are proactive control. Each trial had a length of 2600ms and started with the presentation of a fixation cross (cue presentation) for 300-600 ms. This was followed by the stimuli presentation until a response was given by the participant and could last until 2600ms. If the participant responded sooner, the remaining time was filled with a blank screen until the time was up and a new trial began. The description of each task in the EF test battery can be found in Appendix A. Figure 2 demonstrates one trial example from each task.

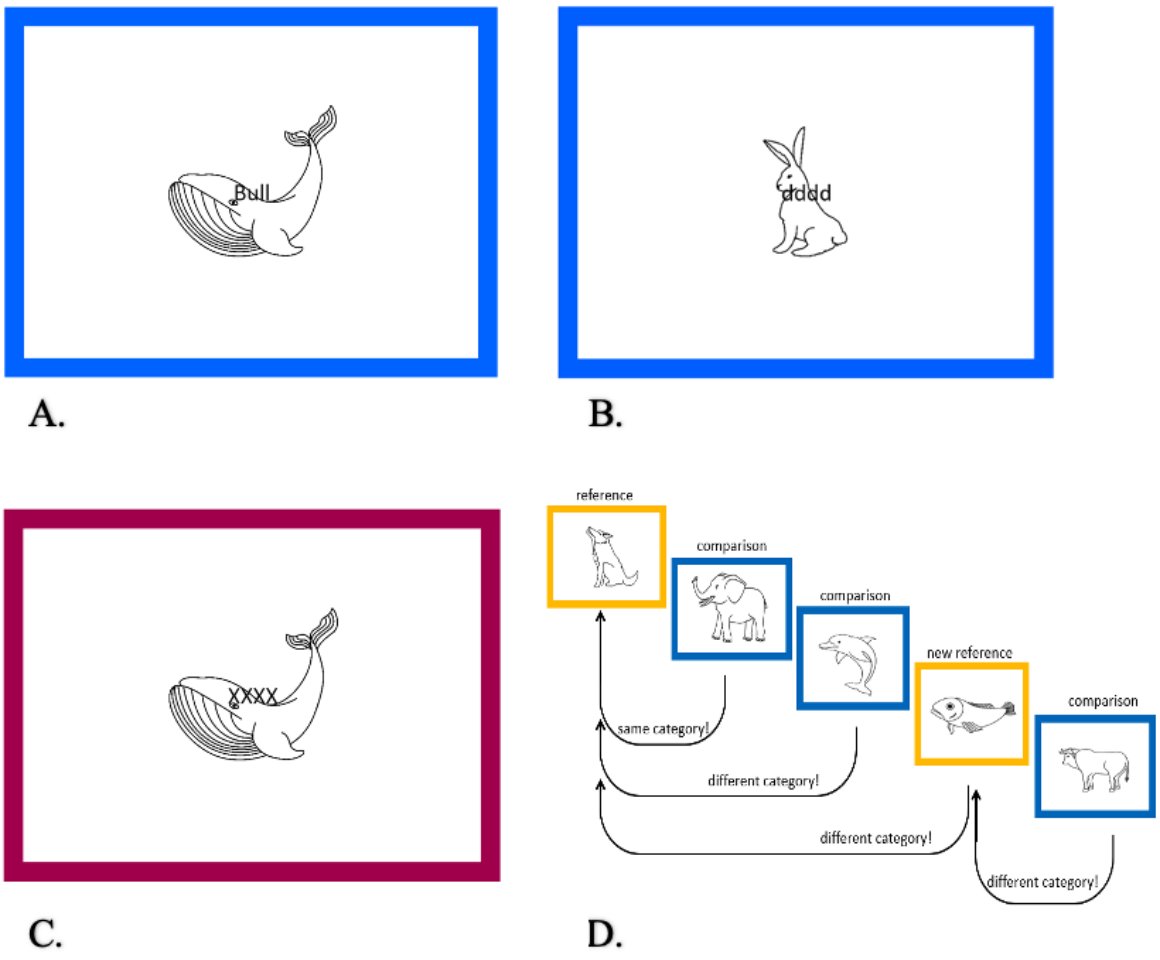

Figure 2: Overview of the EF test battery. (**A**) Demonstrates an example of the trial in the conflict monitoring task, particularly a conflict trial between the picture (sea animal) and word (land animal). (**B**) Shows a stimulus of the set-shifting task, where the picture presents itself as a land animal and the letter strings as lowercase. (**C**) Depicts a trial example of the

response inhibition task, where the participant categorizes the picture as either land or sea animal. In this task, a stop-signal will arise where the participant should withhold their response. (**D**) Exemplifies the reference-back task, where participants memorize the animal category (land or sea) in the reference trial and compares it with a new picture which serves as the new reference.

Procedure - Executive Function Assessment

After allocation to one of the four-week study period and to either NFG or PCG, participants were sent the study information and their individual study ID. The study ID was randomly selected and given to the participant to ensure anonymity. The first questionnaire contained the study information, consent form, demographic information, such as age and gender, and the exclusion criteria. Both groups started with the first cognitive task (conflict monitoring), after which both received two distinct questionnaires: The PCG received the Brief-A (Roth, Isquith, & Gioia, 2005) which measured the subjective everyday EFs, while the NFG received the EAE questionnaire, which assessed neurofeedback expectations. Only the NFG received an additional questionnaire which assessed psilocybin expectation. Thereafter, both groups started with the second cognitive task (set-shifting), and following completion of the second task, the NFG received the Brief-A and the PCG received the psilocybin expectation questionnaire. Both groups started with the third task (response inhibition), and both received two placebo questionnaires to assess susceptibility and optimism. When both groups completed the fourth EF task (working memory updating), they were finished with the pre-measurement. For the post-measurement, the NFG had the same four EF tasks but did not have the questionnaires about psilocybin expectation and placebo. Instead, a set of reflection questions was given to them. The PCG had the same procedure for the post-measurement as the pre-assessment and the sham measurement (‘third

measurement') for the PCG only consisted of the Brief-A questionnaire assessing EFs and a reflection questionnaire about psilocybin.

Tasks and Stimuli – Neurofeedback training

EEG Recording

EEG recordings were obtained using a REFA amplifier (TMSI) and provided 24-bit resolution EEG data with a sampling rate of 256 Hz. The electrodes were placed in accordance with the extended version of the international 10-20 system. Signals were obtained from 32 electrodes from a 64Ag/AgCl cap, however, five electrodes at location Fz, FC1, FCz, FC2, and Cz were used as region of interest for upregulation of the amplitude of fm-theta frequency. The data obtained from the remaining electrodes, is to be used for a connectivity analysis that is beyond the scope of this paper. For this study, the recording was referenced against the nose and FC1 and FC2 were used for eye artefact detection. The impedance level of the electrodes was checked with Charmeleon and kept below 10 kΩ, checked before starting with neurofeedback and changed if needed.

EEG Processing

The EEG data was processed in real-time with an in-house neurofeedback software, NeuroSuite, Huster). During the neurofeedback training, fast Fourier transformations were performed every 200ms with a 2s data window. Windows containing eye artifacts were removed by setting a threshold beforehand, which removed epochs if the spectral band power exceeded said threshold.

Procedure - Neurofeedback

One NF training session consisted of one practice block, a first baseline measure, five neurofeedback blocks, and a second baseline measure (eight blocks à five minutes). After the setting of the EEG cap, participants were instructed to relax and to sit normally during the first two blocks, which also included normal eye blinking. The first two blocks served as a

practice block and a first baseline measure. These instructions were given to the participant so that an eye artefact calibration could be performed before the first neurofeedback task to remove eye artefacts. Then, five neurofeedback trials started in which the participant was instructed to implement cognitive strategies (a list of examples is provided in Appendix C) but were advised to also explore different possibilities for cognitive strategies. Between the tasks, there were breaks and in between each trial the participant was given time to write down the strategies they implemented and rate them on a Likert scale from 1 (not at all useful) to 7 (very much useful). After the neurofeedback training, a second baseline was assessed where the participant was again instructed to rest and not implement any cognitive strategies. This concluded one neurofeedback session. Training sessions on Wednesday and Friday followed the same procedure.

Data preparation and statistical analysis

Behavioral Data

For every participant, reaction time (RT) and accuracy for each task and condition were calculated. Subsequently, repeated measures (RM) analysis of variance (ANOVA)s were conducted for (1) RT and (2) accuracy of all four EF tasks as a within variable ‘Time’, as well as for ‘Condition’, and ‘Group’ was used as a between variable.

EEG Data

The main oscillation of interest was fm-theta bands. For this, the mean theta frequency of every participant throughout the five neurofeedback trials and for every three sessions were calculated. Before analysis, the values were baseline corrected, meaning that the baseline was subtracted from the mean theta power. Several correlations from the first baseline (before the neurofeedback training was administered) were conducted for RT and accuracy of each EF task. Lastly, a RM ANOVA was performed with ‘Session’ as within variable.

Results

The descriptive statistics for RT and accuracy of all four EF tasks are summarized in Appendix B (Table B1 and B2, as well as Figure B1 and B2).

Proactive Tasks

To investigate how the effect sizes from the proactive tasks differ for the NFG and the PCG, four paired t-tests were computed. Significant effects were found when comparing RT for session 1 and session 2 from task switching with $t(9) = 4.701$, $p < 0.001$, Cohen's $d = 1.486$ for the NFG and the PCG with $t(7) = 2.337$, $p = 0.026$, Cohen's d = 0.826. For working memory updating, the results for the NFG yielded $t(9) = 3.691$, $p = 0.002$, Cohen's d = 1.486, and for the PCG with $t(7) = 3.176$, $p = 0.008$, Cohen's d = 1.123.

Both proactive tasks showed significant main effects in both 'Time' and 'Condition'. However no significant interaction effects were found for 'Time*Grouping', 'Condition*Grouping', 'Time*Condition, and 'Tasks*Condition*Grouping' for both groups. Table 1 depicts all the output from the RM ANOVA of set-shifting and working memory updating for RTs.

A.

Set Shifting - RT	*df*	*F*	*p*	η_p^2
Time	1,16	22.669	< .001	0.586
Time*Grouping	1,16	1.876	0.190	0.105
Condition	1,16	95.941	< .001	0.857
Condition*Grouping	1,16	0.440	0.517	0.027
Time*Condition	1,16	1.008	0.330	0.059
Time*Condition*Grouping	1,16	2.900	0.108	0.153

B.

Memory Updating - RT	*df*	*F*	*p*	η_p^2
Time	1,16	22.638	< .001	0.586
Time*Grouping	1,16	0.299	0.592	0.018
Condition	1,16	65.788	< .001	0.804
Condition*Grouping	1,16	3.140	0.095	0.164
Time*Condition	1,16	2.125	0.164	0.117
Time*Condition*Grouping	1,16	1.343	0.264	0.077

Table 1: Output of two RM ANONAs for the proactive tasks. (**A**) presents the RT for set shifting and (**B**), shows the RT for working memory updating.

Figure 3 shows the graphs for RT. Across the proactive tasks, the EF condition has higher reaction times than the no EF condition, which is also true for both the NFG and the PCG. Additionally, the graphs display an improvement in session 2, though for the NFG the slope is steeper in both set-shifting and working memory updating.

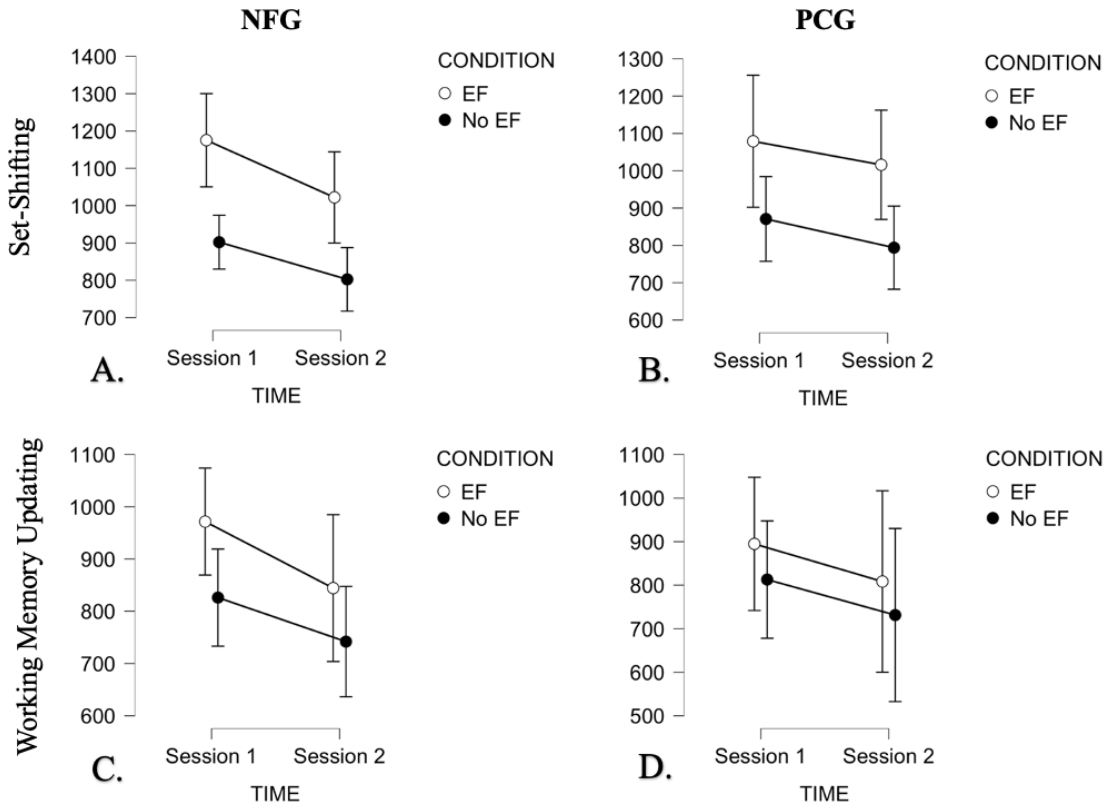

Figure 3: RTs of the proactive tasks, set-shifting and working memory updating, for both groups. (**A**) shows the RT of set-shifting for NFG and (**B**) for PCG. (**C**) shows the RT of working memory updating for NFG and (**D**) for PCG. Note that condition is colored differently and shows for white the EF task and for black the task without the EF component. Error bars display the 95% confidence interval.

Further, four paired t-tests were computed to examine the effect sizes from the accuracy of the proactive tasks for NFG and the PCG. Significant effects were found when

comparing for session 1 and session 2 from task switching with $t(9) = -2.015$, $p = 0.037$, Cohen's $d = -0.637$ for the NFG and the PCG with $t(7) = 0.325$, $p = 0.623$, Cohen's d = 0.115. For working memory updating, the results for the NFG yielded $t(9) = -0.425$, $p = 0.340$, Cohen's d = -0.134, and for the PCG with $t(7) = 1.496$, $p = 0.911$, Cohen's d = 0.529.

Table 2 depicts all the output from the RM ANOVA of set shifting and working memory updating for accuracy. In similar vein to RTs, accuracy showed a significant main effect for 'Condition' for both groups, but no significant main effect was found for 'Time'. Moreover, no significant interaction effects were found for 'Time*Grouping', 'Condition*Grouping', 'Time*Condition, and 'Tasks*Condition*Grouping' for both groups.

A.

Set Shifting - AC	*df*	*F*	*p*	η_p^2
Time	1,16	1.696	0.211	0.096
Time*Grouping	1,16	2.796	0.114	0.149
Condition	1,16	72.690	< .001	0.820
Condition*Grouping	1,16	0.090	0.768	0.006
Time*Condition	1,16	0.572	0.460	0.035
Time*Condition*Grouping	1,16	1.231	0.284	0.071

B.

Memory Updating - AC	*df*	*F*	*p*	η_p^2
Time	1,16	0.753	0.398	0.045
Time*Grouping	1,16	3.870	0.067	0.195
Condition	1,16	26.297	< .001	0.622
Condition*Grouping	1,16	2.912	0.107	0.154
Time*Condition	1,16	0.122	0.732	0.008
Time*Condition*Grouping	1,16	1.164	0.297	0.068

Table 2: Output of two RM ANONAs for the proactive tasks. (**A**) presents the accuracy for set-shifting and (**B**), shows the accuracy for working memory updating.

Figure 4 shows the graphs for accuracy. The EF condition has lower accuracy than the no EF condition, which can be seen for both groups and both proactive tasks. Further, the graphs display only an improvement in session 2 for set-shifting, where the NFG seems to improve more compared to the PCG. For working memory updating, the NFG stays stable (i.e. no improvement can be seen), whereas the PCG has lower accuracy in session 2.

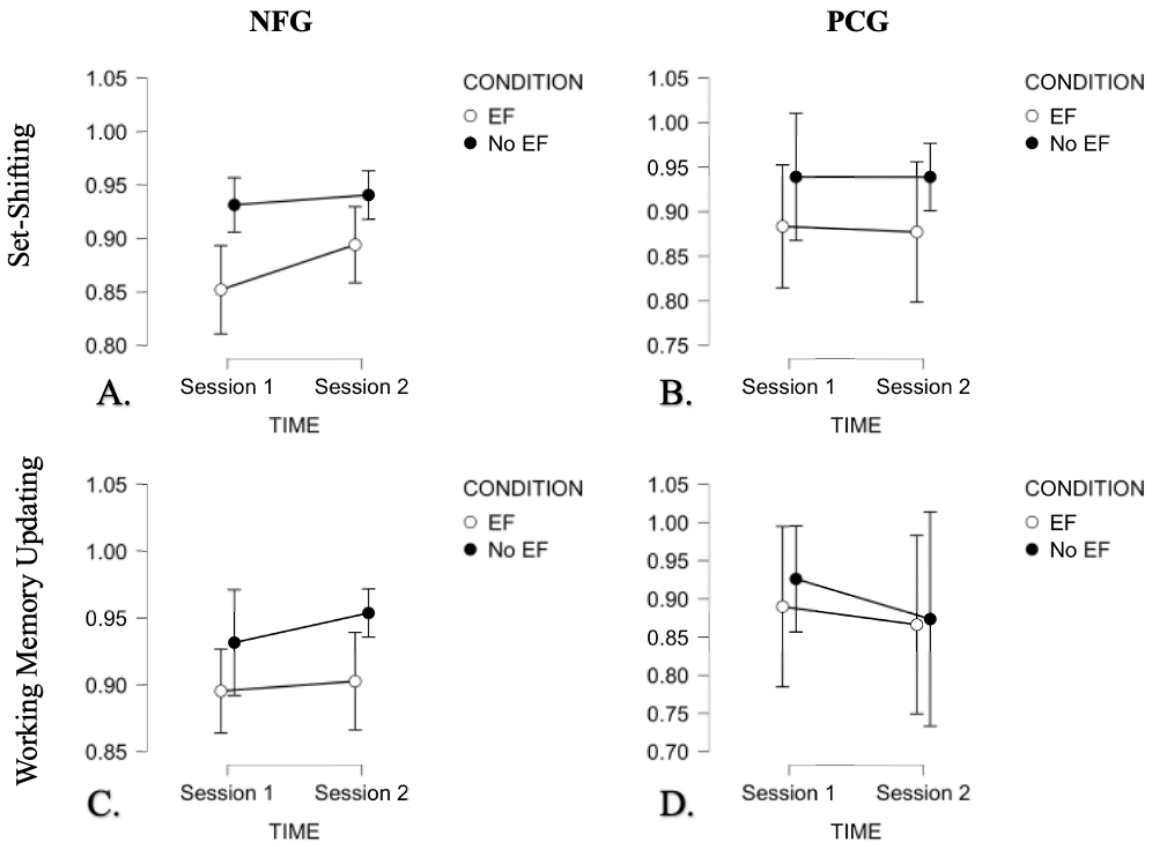

Figure 4: Accuracy of the proactive tasks, set-shifting and working memory updating, for both groups. (**A**) shows the accuracy of set-shifting for NFG and (**B**) for PCG. (**C**) shows the accuracy of working memory updating for NFG and (**D**) for PCG. Note that condition is colored differently and shows for white the EF task and for black the task without the EF component. Error bars display the 95% confidence interval.

Reactive Tasks

To investigate how the effect sizes differ from the EF conditions for conflict monitoring and response inhibition for both groups, four paired t-tests were computed. Significant effects were found when comparing RT for session 1 and session 2 from conflict monitoring with $t(9) = 5.489$, $p < 0.001$, Cohen's $d = 1.736$ for the NFG and the PCG with $t(7) = 1.578$, $p = 0.079$, Cohen's d = 0.558. For response inhibition, the results for the NFG yielded $t(9) = -0.207$, $p = 0.580$, Cohen's d = -0.065, and for the PCG with $t(7) = -0.269$, $p =$

0.764, Cohen's d = -0.269. Further, another two paired t-tests to test differences for accuracy were computed. Significant effects were found when comparing accuracy for session 1 and session 2 from conflict monitoring with $t(9) = -1.014$, $p = 0.169$, Cohen's $d = -0.321$ for the NFG and the PCG with $t(7) = -2.317$, $p = 0.029$, Cohen's d = -0.819.

For RT, only conflict monitoring showed significant main effects in both 'Time' and 'Condition', while response inhibition only had a significant main effect in 'Condition'. No significant interaction effects were found for 'Time*Grouping', 'Condition*Grouping', 'Time*Condition, and 'Tasks*Condition*Grouping' for both groups. Similarly, conflict monitoring showed significant main effects for 'Time' and 'Condition' for accuracy, as well as a significant interaction effect for 'Time*Grouping'.

A. Conflict Monitoring – RT

	df	*F*	*p*	η_p^2
Time	1,16	18.421	< .001	0.535
Time*Grouping	1,16	0.699	0.415	0.042
Condition	1,16	74.562	< .001	0.823
Condition*Grouping	1,16	0.387	0.543	0.024
Time*Condition	1,16	0.008	0.932	0.004
Time*Condition*Grouping	1,16	0.088	0.771	0.005

B. Response Inhibition – RT

	df	*F*	*p*	η_p^2
Time	1,16	0.003	0.955	0.002
Time*Grouping	1,16	0.002	0.962	0.001
Condition	1,16	35.877	< .001	0.692
Condition*Grouping	1,16	0.800	0.384	0.048
Time*Condition	1,16	1.862	0.191	0.104
Time*Condition*Grouping	1,16	0.477	0.500	0.029

C. Conflict Monitoring – AC

	df	*F*	*p*	η_p^2
Time	1,16	18.898	< .001	0.542
Time*Grouping	1,16	3.212	0.092	0.167
Condition	1,16	33.371	< .001	0.676
Condition*Grouping	1,16	0.480	0.498	0.029
Time*Condition	1,16	0.507	0.487	0.031
Time*Condition*Grouping	1,16	0.713	0.411	0.043

Table 3: Output of three RM ANONAs for the reactive tasks. (**A**) presents the RT for conflict monitoring, (**B**) shows the RT for response inhibition, and (**C**) depicts the accuracy for conflict monitoring.

Across the reactive tasks, the EF condition has higher RTs and lower accuracy than the no EF condition, which is also true for both the NFG and the PCG. Additionally, the graphs only display an improvement in session 2 for conflict monitoring for both RT and accuracy, while response inhibition stays stable.

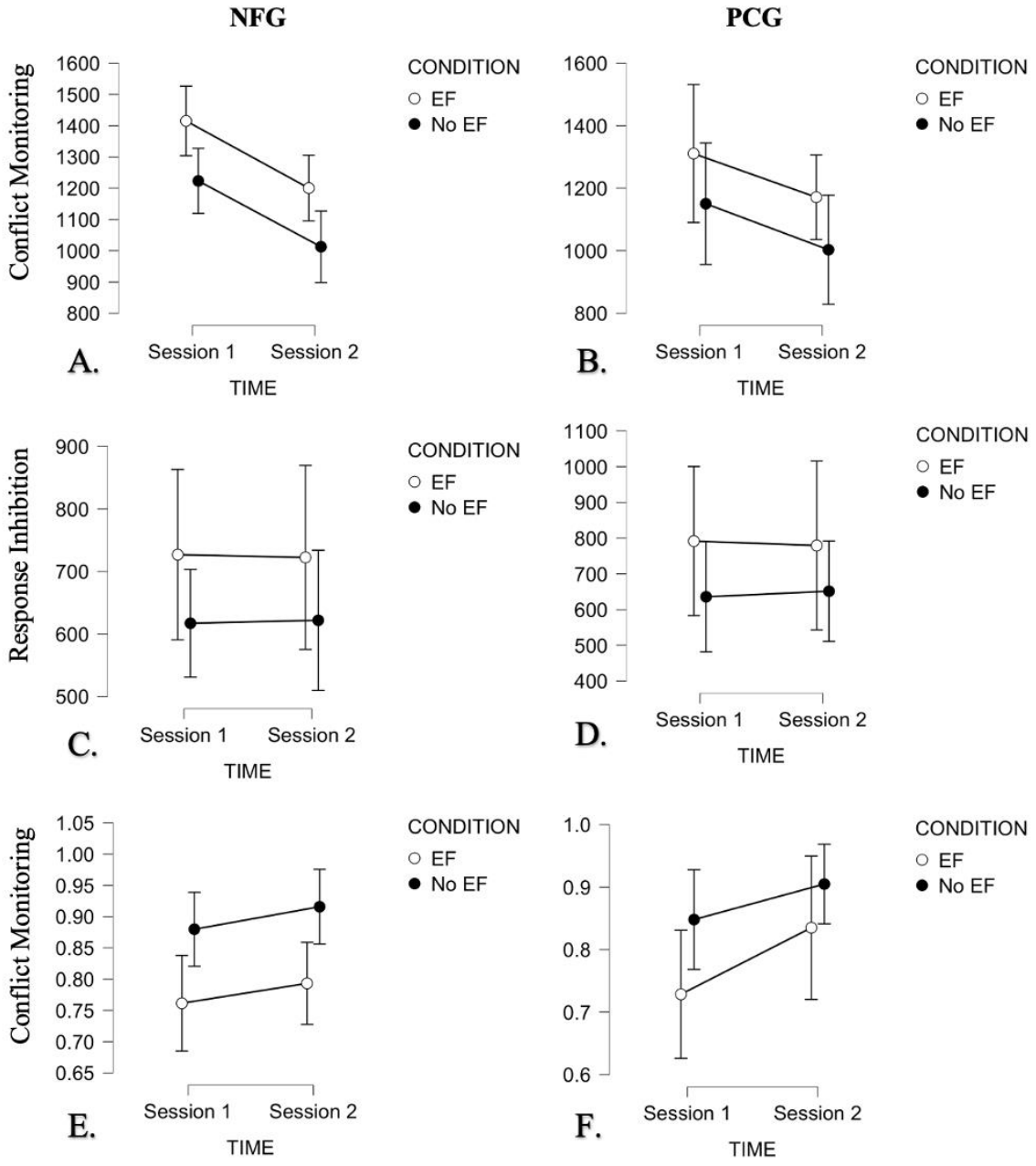

Figure 5: RTs and accuracy of the reactive tasks, conflict monitoring and response inhibition, for both groups. (**A**) shows the RT of conflict monitoring for NFG and (**B**) for PCG. (**C**) shows the RT of response inhibition for NFG and (**D**) for PCG. (**E**) shows the

accuracy of conflict monitoring for NFG and (**F**) for PCG. Note that condition is colored differently and shows for white the EF task and for black the task without the EF component. Error bars display the 95% confidence interval.

Analysis of EEG Data

To investigate mean differences in theta oscillations between each neurofeedback session, one RM ANOVA was used. To ensure more precise results, the results were firstly baseline corrected and yielded non-significant results ($F(2, 18) = 2.514$, $p = 0.109$). Secondly, correlations with each EF task and with the first baseline measure (before the neurofeedback training) were conducted.

Proactive tasks. For the RT of set-shifting, no significant results were found with $r(8)= 0.315$, $p = 0.375$ as well as for working memory updating ($r(8)= 0.028$, $p = 0.938$). Similarly, accuracy found no significant effect for set-shifting ($r(8)= -0.017$, $p = 0.962$), but for working memory updating with $r(8)= 0.879$, $p < 0.001$.

Reactive tasks. In regards to the RT, no significant results were obtained for conflict monitoring ($r(8)= 0.117$, $p = 0.747$) as well as for response inhibition ($r(8)= 0.215$, $p = 0.551$). However, for accuracy, significant effects were found for conflict monitoring ($r(8)= 0.689$, $p = 0.028$).

Discussion

The main goal of neurofeedback, and more broadly for cognitive training, is to enhance certain cognitive skills, or in our case self-regulate theta oscillations that are indicative of EFs, and through training be able to generalize these improvements to everyday life. This study was one of the first to our knowledge to explore the effects of multimodal treatments of neurofeedback and psilocybin on EFs. The results suggest a trend that proactive tasks are facilitated by neurofeedback training. More specifically, it seems that set-shifting performed better than working memory updating. For the reactive tasks, there was no

conclusive trend that could be observed, and the results are rather mixed. For example, a significant interaction effect ('Time*Grouping') for conflict monitoring for accuracy was found suggesting that the NFG was significantly different from the PCG. In general, the results from the effect sizes infer that the NFG had a bigger mean difference in RT and accuracy than the PCG for both proactive and reactive tasks. The results from the correlations overall showed inconclusive results, and it seems that no prediction could be made from a fm-theta baseline measure.

Overall, like our hypothesis suggested, it was shown that improvements across proactive control tasks were facilitated by our intervention, but EFs relying on reactive control were not significantly improved by neurofeedback training. More specifically, the NFG showed more improvement on set-shifting than in the task assessing working memory updating. This may suggest that, although this study could not find significant improvement on working memory updating, it may have stemmed from the fact that the power was too low to find an effect. Further, this reference-back task was slightly changed compared to the working memory updating task used previously (i.e. with Enriquez-Geppert et al., 2014). This modification was done to improve the working memory updating aspect by implementing a 'keep track' condition that should allow the control process to function. However, a possible explanation may be that our 'repeat' condition may strain the working memory space, and this may not facilitate the actual updating component but rather inhibit it by leading the participant to be stuck on that trial longer than usual. Nonetheless, studies have found that upregulation of fm-theta amplitude was associated with facilitation of working memory updating (Eschmann et al., 2020; Enriquez-Geppert et al. 2014).

In similar vein, a recent meta-analysis from Viviani and Valesi (2021) found that neurofeedback training had mixed results. Improvements on proactive control processes were observed in some studies but others with similar methods obtained improvements on reactive

control. In the analysis, both groups showed better task performance in the post measurement compared to the pretest, which was to be expected and may be explained by repetition of the tasks. There was also a clear difference between the conditions implementing the EF control, which had higher RT and less accuracy than conditions which did not implement EF control. As such, the central role of the FPN, and specifically the MCC, becomes clear when investigating the involvement in regulating cognitive control functions because the MCC picks up activity when effortful cognitive functions (i.e. EFs) are required. More specifically, the MCC detects the increased cognitive load and power needed when engaging in EF tasks and generates changes in the DLPFC and PFC to increase cognitive control (Kerns, 2006). However, these results and those from previous studies may indicate that perhaps it is specifically the proactive tasks which are mediated by the MCC since those are the ones which seem to benefit the most from neurofeedback training. Due to the multi-facetted nature of EFs, it may be that different control processes are mediated by different networks or that just several modalities like different frequencies must be trained to show the expected results. Since the FPN encompasses many structures, it would be worthwhile to investigate whether specific subnetworks are responsible for different cognitive functions. Nonetheless, for this study is seems that though a trend can be observed that neurofeedback facilitated some neuroplastic changes since bigger mean differences could be seen in the NFG.

In general, when assessing the proactive tasks, the NFG performed better than the PCG. Interestingly, when comparing effect sizes from previous studies, the effect sizes from this study were higher than those found in previous studies (Enriquez-Geppert et al., 2014; Eschmann & Mecklinger, 2021) as well from a meta-analysis (Viviani & Vallesi, 2021). These results may suggest that not only the neurofeedback training is responsible to improve the behavioral effect of proactive EFs, but that combining psilocybin may have an additive effect to neurofeedback. However, because this study did not employ an active control group,

it is impossible to distinguish the effects from neurofeedback and psilocybin. In this study, a micro-dose of psilocybin was not able to significantly improve control processes but did show an effect when comparing the post-measurement to the pre-measurement from both groups. Thus, a transfer effect of cognition on behavior can be observed because larger mean differences are constantly observed throughout the NFG. This strengthens the notion that multimodal approaches which target several domains at once have additive/synergistic effects than just neurofeedback by itself. Moreover, the results exemplify that perhaps our study had too low power to find an effect or that the unstable dose of psilocybin may have contributed to the inconclusive results.

Previous studies have found an increase in functional connectivity after neurofeedback (Zhao et al., 2019), as well as gray and white matter features around those areas predicting the outcome of neurofeedback training (Ninaus et al., 2015). A similar argument was tested whether baseline fm-theta amplitude was predictive of EF task success. Very mixed and inconclusive findings resulted from the correlation analysis and the results did not indicate a predictive value with baseline fm-theta measurement. However, it may be noted that although the participants had not yet started with the neurofeedback training, they took a psilocybin micro-dose two hours before which may have obstructed the real baseline fm-theta measure of participants. Since psilocybin has been found to reduce DMN connectivity as well as increases connectivity in networks associated with higher cognitive processes, such as the FPN, our baseline measures are more likely to be higher than usual. A study from Barrett et al. (2020) suggested that this may be mediated by reducing claustrum functional connectivity within these networks.

Limitations

When reviewing the results and implications of this study, a few limitations must be taken into consideration. It may be noted that an important limitation is the fact that this study

employed a no-intervention group (i.e. PCG). For that reason, being able to make casual and accurate claims, may be limited in this study. One of the risks of the assessment of a PCG is that placebo effects cannot be ruled out completely. Despite this study implementing placebo questionnaires to assess certain traits that are related to experience to the intervention, we cannot fully disclose if expectancy to the intervention of neurofeedback or perhaps to the psychoactive truffles may have been interfering with the results observed in the improvement of the neurofeedback sessions.

Moreover, it is important to highlight that this study had a small sample size (n = 18) which due to the time restrictions, data collection could not be extended. This low sample size adds a high amount of variation that normally can be accounted for if more people participate in the study. Similarly, it may be noted that our cognitive assessment was conducted online, and despite an experimenter was always being present during these sessions and outliers were removed, it could not be verified how concentrated participants engaged in the EFs tasks.

Recommendations and Future research

Future research should follow up on this potential treatment but should implement several steps to ensure more reliable results. Firstly, individual baseline fm-theta should be measured before the participants are administered psilocybin since the ingestion of psilocybin two hours before the neurofeedback training could have interfered with baseline measurement and therefore not provided an accurate measure of the fm-theta baseline. Moreover, substances, such as mycelium containing psilocybin, which are more constant in their concentration of psilocybin would yield more reliable results because participants would be administered the same dosage throughout the experiment, compared to this study where we could only guess the dosage based on the estimation given by the providers of the truffles. This of course, adds unwanted variation to the experiment. Furthermore, implementing more groups with different doses of psilocybin as well as employing an active control group could

rule out placebo effects more reliably and provide more accurate results if more psilocybin could facilitate (or inhibit) transfer effects on cognition. The fact that reactive control processes do not seem to be facilitated by upregulating fm-theta oscillations, and by that specifically by the MCC, suggests that other (sub-)networks need to be involved. Although control processes may be executed from the FPN, our region of interest may have not fully captured all the interconnected areas responsible for all EFs. A disruption in the FPN specifically has widespread consequences and has been linked to a myriad of neuropsychological and psychiatric disorders, including depression, schizophrenia and even Alzheimer's disease (Menon, 2011). Although all these disorders may encompass cognitive problems, these disorders are widely different from each other and thus their cognitive ability may also not be impaired in the same way. Since psilocybin and neurofeedback show promising effects on neuroplasticity, further investigation on how exactly these mechanisms work and what (sub-)networks rely on different control processes would improve the ability to target specific problems more accurately. Successful treatment options rely on future research to pave the way for improved rehabilitation tools for clinical practice. Although this study is far from that, it introduces a new mechanism underlying neuroplastic changes that may help improve executive control.

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Appendix A

Conflict Monitoring. The principle of the Stroop task was used, where the presented stimuli consisted of a picture and the name of an animal, and the goal is to categorize the stimuli according to their category (either land or sea animal). A trial could consist of two different options: the animal and the animal's name present the same category (e.g. a picture of a whale, with the name 'whale'). In this case, a congruent trial is presented to the participant. In an incongruent trial, the picture and the name of the animal presents itself which does not align with the two categories (Figure 2). The participant responds to either the word or the picture according to the color of the frame signaling word categorization or picture categorization. Hence, there are four different task versions. In total there are 140 trials (four blocks á 35 trials) with an equal amount of congruent and incongruent trials.

Set Shifting. A task switching task based on the principle of the Wisconsin card sorting task was used. Similar to the conflict monitoring task, participants have to categorize the presented stimuli, however, for this task two sets of different categories are presented, namely (1) the category of land or sea animals and (2) the string of letters that is either lowercase or uppercase (Figure 2). Participants know to respond to which category based on the colored frame, making it eight different task versions. In total, there are 172 trials where the first 32 serve as a baseline since they are unmixed, meaning that the participant responds to one of the forms (i.e. no task switching element). In the rest of the 140 trials (divided by four blocks), there is a 4:6 ratio of switch to no-switch trials respectively.

Response Inhibition. Here, the stop-signal task was used. The participant must indicate the stimuli based on their category, which are comprised of land and sea animals (Figure 2). In stop trials, a stop-signal delay is presented indicating to the participant that they are asked to withhold a response. However, this delay appears when the participant has already started with an action and required them to stop said action. The length of the stop-

signal delay is adapted according to the participants response meaning that if in the previous task the participant successfully stopped their response, the response window is prolonged so that the participant is more likely to not hold the response. However, if the participant responded in the stop trial, the stop-signal delay is shortened, making a successful action (stops the response) more likely. The stop-signal delay is changed so that participants have a 50% to inhibit their response action.

Working Memory Updating. Lastly, the reference-back task was used, in which two types of trials may occur: a reference condition and a comparison condition. For both types, stimuli from either a land or a sea animal were presented, and the participant had to remember which animal type was presented in the reference trial. The participant had to indicate whether the animal from the reference trial was from the same or a different category and following a response, the new animal (not the one from the last reference) was used as a new reference for the next trial (Figure 2). To differentiate between reference and comparison trials, colored frames were used to indicate to the participant which condition was asked. In total, there were 240 trials divided into four blocks and there was a 3:1 ratio of comparison versus reference trials respectively. It was set beforehand, that (1) no two reference trails follow each other, (2) at least one comparison trial is in between, and (2) there cannot be more than five comparison trials after each other.

Appendix B

Session 1

Group			PCG	EXP
RT	CM	*Conflict*	1310,93	1415,32
		No Conflict	1150,39	1223,47
	MU	*Updating*	894,85	971,70
		No Updating	812,90	826,27
	IN	*Go*	791,93	726,96
		Stop	330,20	264,35
	SS	*Repeat*	870,84	902,07
		Switch	1079,08	1175,29
Accuracy	CM	*Conflict*	0,66	0,72
		No Conflict	0,85	0,87
	MU	*Updating*	0,89	0,90
		No Updating	0,93	0,93
	IN			
	SS	*Repeat*	0,94	0,93
		Switch	0,88	0,85

Table B1: Shows the descriptive statistics of the pre-measurement of each EF task for both RT and accuracy, and for both groups.

Session 2

Group			PCG	EXP
RT	CM	*Conflict*	1171,24	1200,43
		No Conflict	1003,20	1012,68
	MU	*Updating*	808,40	844,41
		No Updating	731,37	741,99
	IN	*Go*	779,53	722,49
		Stop	294,50	245,27
	TS	*Repeat*	793,97	802,43
		Switch	1016,05	1022,02
Accuracy	CM	*Conflict*	0,83	0,78
		No Conflict	0,90	0,92
	MU	*Updating*	0,87	0,90
		No Updating	0,87	0,95
	IN			
	TS	*Repeat*	0,94	0,94
		Switch	0,88	0,89

Table B2: Shows the descriptive statistics of the post-measurement of each EF task for both RT and accuracy, and for both groups.

Proactive tasks

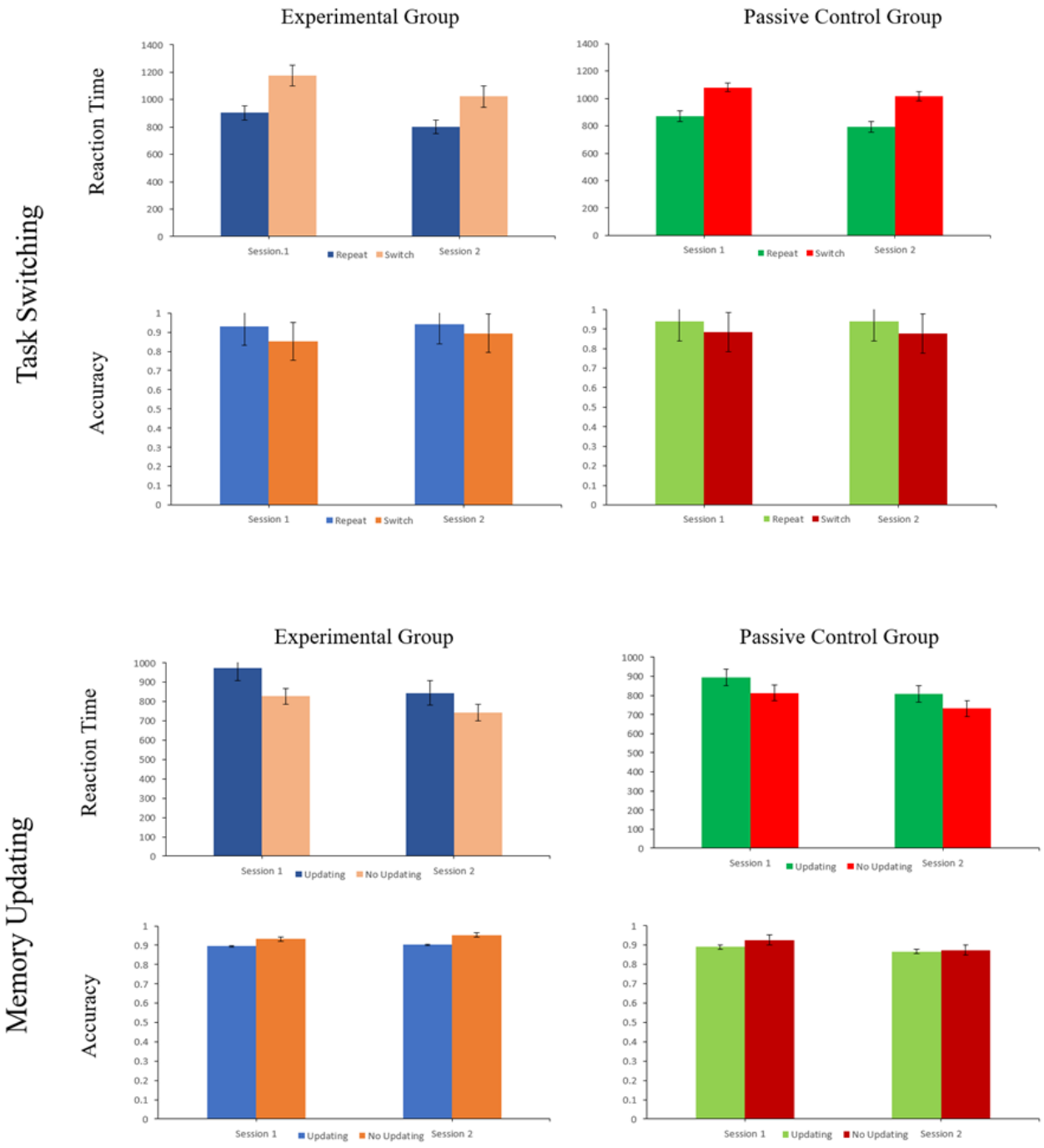

Figure B1: Bar graphs of the proactive tasks for the NFG and the PCG.

Reactive tasks

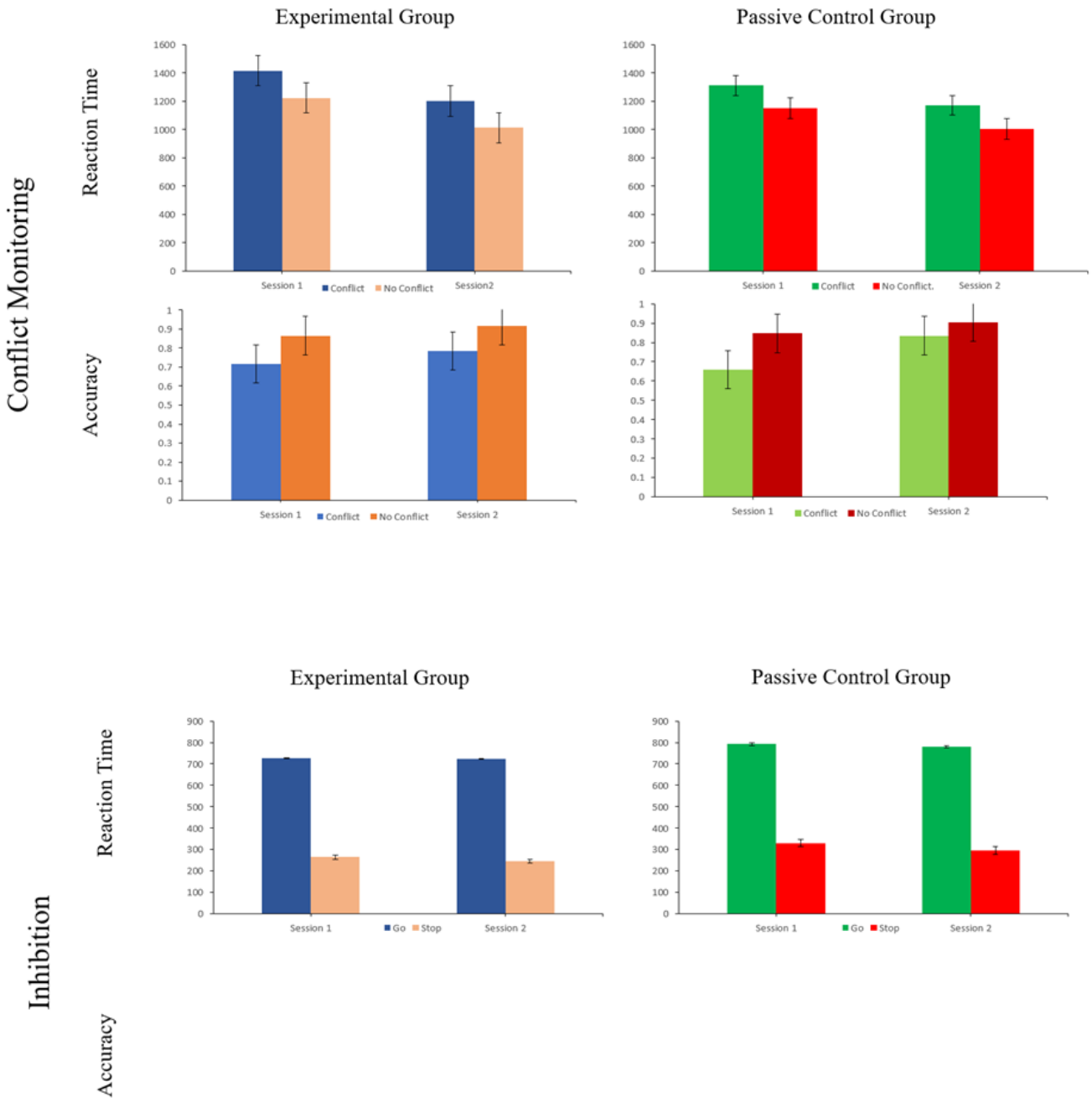

Figure B2: Bar graphs of the reactive tasks for the NFG and the PCG.

Appendix C

Possible Neurofeedback Strategies

Mental tasks, such as**:**

- Perform arithmetic/calculation tasks
- Recall memory content (e.g. what did I eat this week or what people did I meet last month?)
- Planning (e.g. what will I do next week?)
- Mentally rotate objects (e.g. imagine rotating a cup 360 degrees)
- Mentally navigate (through familiar buildings or streets)
- Allowing spatial attention to wander (e.g. moving to different areas without losing sight of the space (from one side to the other))

Relaxation, e.g. through concentration on breathing

Imagining emotions (positive/negative)

Recall memories/imagining situations

- Family members (parents, siblings, grandparents)
- Friends and acquaintances
- Partners

Auditory imaginations, e.g. imagining sounds or music

Cheering on the red square

Imagining movement or activities

- Arm or foot movements
- Playing sports
- Singing
- Movie watching

Thoughts about nature/imagination of nature

- Imagine it raining
- Imagine a sunset
- Imagine certain landscapes
- Imagine a journey

Thoughts/imagining everyday things

- Cooking or eating
- Going shopping
- Cleaning