Neuroenhancement or Neuroenchantment?: An Investigation of Psilocybin-Assisted Neurofeedback and Placebo.

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Abstract

Objective

Neurofeedback is a treatment protocol partially moderated by neuroplasticity. Putting the brain in an increased neuroplastic state through a psilocybin microdosing regime, an increased response to neurofeedback can be expected. This being said, both neurofeedback and psilocybin microdosing are contentious. For this reason, this study will evaluate the efficacy of combining neurofeedback and psilocybin while considering the implications of placebo in the intervention.

Method

Two distinct groups participated in this study, one group exposed to the entire intervention and one passive control group. The experimental group received a 3-day neurofeedback session and microdosed for 2 weeks. Both groups took a cognitive battery assessing working memory updating, response inhibition, set-shifting, and conflict monitoring to measure executive function improvements.

Results

A nonsignificant difference p=0.180 with a moderate to large effect size, d= 0.655 was found between experimental and passive control group in improvement in executive function task reaction time, a nonsignificant difference p=0.839 with effect size d=0.098 was found in executive function task accuracy improvement. A nonsignificant improvement p=.110, effect size $\eta 2p$=0.218, between sessions in the experimental group was shown. PRL had moderate to strong correlations with neurofeedback improvement r=.370, executive function reaction time r=.244 and executive function accuracy r=.245.

Conclusion

Psilocybin-assisted neurofeedback is a novel therapeutic protocol with much promise. However, much research is needed to understand the intervention's full capabilities and to understand the role of placebo in eliciting improvement during the intervention.

Neuroenhancement or Neuroenchantment?: An Investigation of Psilocybin-Assisted Neurofeedback and Placebo.

The topics of neurofeedback (NF) and psilocybin microdosing have individually been debated in recent years. Both topics have illustrated a mixture of illuminating results and disappointing outcomes, leading to a clash between schools of thought. Many argue that either of the treatment options are efficacious and should be used more often in clinical practice (Griffiths et al., 2016; Rootman et al., 2022), while others argue that both treatments are placebo (Kober et al., 2018; Marschall et al., 2022; Schönenberg et al., 2017). However, one thing is for certain, both treatments have large implications for clinical practice, with NF offering a way to address executive dysfunction (Enriquez-Geppert et al., 2013) and microdosing offering many cognitive benefits such as increased mood and upregulated cognitive abilities (Rootman et al., 2022). For these reasons, this study will combine the two treatment options and attempt to understand the role of placebo in the intervention as a whole.

To begin, it is important to understand what this protocol will be targeting; Executive Functions (EFs). EFs are an integral part of being human, they are the underlying skills that allow us to make complex decisions in split seconds. It has been established that EFs can be broken down into four components; working memory updating, response inhibition, set-shifting, and conflict monitoring (Miyake et al., 2000). These skills are extremely important for success in a person's day-to-day life with EFs correlating with academic success, social functioning, and successful ageing (Enriquez-Geppert, Huster, & Herrmann, 2013). Therefore, research has begun on how EFs can be improved in both clinical and non-clinical cases (Hunter & Sparrow, 2012).

Psilocybin-assisted NF is a novel therapeutic protocol, which attempts to improve EFs, in which participants undergo NF while also following a psilocybin microdosing regime. Logically

speaking, it would make sense to combine these two interventions as they individually have been hypothesized to illustrate efficacy in promoting increased scores in tests of EFs, cognitive control, or memory (Magaraggia et al., 2021; Wang & Hsieh, 2013; Yu et al., 2020). However, more accurately, combining these interventions comes down to one factor: neuroplasticity. NF's underlying mechanisms are moderated by plasticity levels (Loriette et al., 2021), while psilocybin is a neuroplastic drug (de Vos et al., 2021). In theory, psilocybin use should upregulate plasticity levels (Catlow et al., 2013; Jefsen et al., 2021) in the participants creating an environment in which greater benefit can be found in the NF. This should lead to greater efficacy during the NF training and enduring behavioural outcomes following the treatment.

Furthermore, this neuroplasticity increase should help target a large issue in NF research; the fact that 30% of participants show no response to the treatment whatsoever (Becker et al., 2022). The neuroplastic environment should open neurofeedback up to some of these non-responders and possibly allow responders to improve further. To understand why this happens, it is important to understand how NF and plasticity relate independently to psilocybin. The type of plasticity NF takes advantage of is referred to as perturbative physiological plasticity, in short, it effectively means that Hebbian learning occurs based on internal or external events (Orndorff-Plunkett et al., 2017). By implementing psilocybin, more opportunities for this Hebbian-based activation can occur, which in turn should create more neural connections. This influx in connections has been shown to aid in some of the issues that can create neurofeedback nonresponse. Furthermore, this neuroplasticity ties directly to some mechanism of NF nonresponse, factors such as attention, motivation, and mood have been shown to be particularly important in predicting NF response (Kadosh & Staunton, 2019) while neuroplasticity has been tied to increased mood and motivation (Drevets, 2004). Furthermore, the underlying white matter

volume and structure of the mid cingulate cortex (MCC) has been shown to act as a predictor variable for responsiveness of neurofeedback training (Enriquez-Geppert et al., 2013). By inducing neuroplastic changes in this region it is possible that participants with nonresponsive morphology could, through Hebbian connectivity changes, see increased white matter in this region and therefore be more likely to respond to neurofeedback.

However, with this, these two treatment protocols have never been combined. For this reason, it is vital to investigate the effects of combining these two treatments and attempting to understand if the proposed mechanisms will actually work or if the effect produced will be due to placebo.

NF and Executive Functions

NF is the process of attempting to alter the electrical activation of one's brain by employing a host of cognitive strategies whilst receiving real-time feedback as to the efficacy of the strategies. This is done through neuroimaging techniques such as fMRI or Electroencephalogram (EEG; Marzbani et al., 2016). EEG operates by reading and printing electrical activity within the brain. One major benefit of EEG is its strong temporal resolution, meaning that the data being produced reflects changes in the brain in (more or less) real-time (Law et al., 1993). During the NF session, the EEG data is online processed, analysed, and depicted back to the participant giving them an indication as to their brain activation relative to baseline.

NF can target a variety of brain oscillations with different functional outcomes (Marzbani et al., 2016). However, when considering higher-order cognitive function, the frontal midline (FM) is of extreme importance (Ishii et al., 1999). Specifically, theta oscillations (4-8HZ) can be detected at this FM. Theta oscillations are thought to be generated in the MCC, which is an area

of particular interest in reference to cognitive functioning (Wang et al., 2005).The MCC is one of the brain regions part of the cognitive control network (Vogt, 2016). It is a highly interconnected structure that appears to have important roles in communicating with the other structures involved in this network, such as the parietal cortex (PC) and the dorsolateral prefrontal cortex (dlPFC). Seemingly, the MCC monitors and communicates conditions requiring cognitive control to PC and dlPFC (Niendam et al., 2012). Through the MCC, the PC provides the dlPFC with information about the importance of stimuli and learned responses to said stimuli (Niendam et al., 2012). With this, the dlPFC, which is an area of the brain that has involvement in many cortical networks, can orchestrate thought, and purposeful action, and drive attentional processes (Miller & Cohen, 2001). Due to FM theta's involvement, theta oscillations are often crowned "the working language of the brain" and through this many studies have illustrated that monitoring of the power of theta oscillations and the efficiency in which the MCC communicates with the aforementioned brain regions to be strong indicators of efficacious executive functioning (Enriquez-Geppert et al., 2014). Studies have shown that upregulation of theta in the FM can address deficits in EFs. For example, upregulation of theta through NF has illustrated improvements in many tasks requiring EFs; conflict monitoring (Oehrn et al., 2014) and mental set-shifting (Enriquez-Geppert et al., 2014). Thus, in many settings, it has been elucidated that targeted regulation of these waves can lead to benefits in global executive functioning in both clinical and non-clinical populations (Garcia Pimenta et al., 2021; Yu et al., 2020)**.**

Psilocybin, Executive Functions, and Psilocybin-Assisted NF

As mentioned above, NF's efficacy is theorized to be partially moderated by neuroplasticity. For this reason, use of a neuroplasticity-promoting agent like psilocybin could be beneficial. Psilocybin is a psychedelic drug that binds to the 5-HT2A serotonin receptors.

Clinical use of the drug has illustrated many cognitive benefits such as alleviation of depression (Griffiths et al., 2016), smoking cessation (Griffiths et al., 2016; Johnson et al., 2017)) and anxiolytic effects (Griffiths et al., 2016). These behavioural changes are accompanied by physiological alterations, such as neuroplastic and neutropenic changes, alterations in blood flow, and connectivity changes. Connectivity changes have been recorded in the MCC, the dlPFC, the PC, and other interrelated parts of the default mode network (DMN) and the central executive network (CEN). The reason these specific networks are important, is because they all play a role in EFs (Hunter & Sparrow, 2012) and, as was mentioned earlier, efficacious communication between these brain areas is the cornerstone of EFs. Psilocybin use promotes increased internetwork communication and decreased network modularity (Daws et al., 2020), meaning that it may allow said structures to change how they communicate and therefore influence ability to engage in EF.

These changes in internetwork connectivity are moderated by neuroplastic alterations. Multiple studies have illustrated mechanisms of neuroplasticity following psilocybin use. For example, in mice, one treatment of psilocybin has been shown to induce persistent and rapid growth of dendritic spines in the frontal cortex (Shao et al., 2021). Further, levels of Brain-Derived Neurotrophic Factor, a plasticity-promoting protein, are increased following a regime of psilocybin in mice (de Vos et al., 2021). The predominant reason that these physiological changes are so integral is that their consequences tend to be enduring, i.e., they persist following the end of a trial. Studies have reported alterations in global brain connectivity up to 3 months following a single dose and changes in the CEN observable up to 1 week following an intervention (McCulloch et al., 2022). In addition to this, these enduring effects have been illustrated in cognitive flexibility following a single dose of psilocybin (Doss et al., 2021).

The persisting nature of this plasticity-induced cognitive flexibility is the crux of the intervention. The psilocybin is being used to create a neuroplastic environment in which the participant's brain is more adaptive to the task they are engaging in. Combining this with NF will allow the participant to self-regulate their neural oscillations more effectively and therefore increase the cognitive benefit of the NF. Therefore, the primary goal behind the usage of psilocybin is to facilitate the cognitive benefits of NF.

Placebo, NF, and Microdosing

When considering the effects of interventions such as this, it is important to understand how environmental and social factors can influence a study's outcome. In the case of NF and microdoses of psychedelic drugs, a common concern is placebo. Multiple studies have attempted to argue that the effects produced by both treatment options are solely due to placebo (Marschall et al., 2022; Schönenberg et al., 2017). However, with how topical NF and psilocybin are, there is lots of contradictory literature, thus it can be difficult to fully understand the role of placebo in either treatment protocol.

Placebo can be defined as a response to a sham substance or treatment that produces effects in lieu of an actual intervention. It is used to control for the social factors surrounding an experimental situation that could produce improvements or results that cannot be attributed to the intervention. Oftentimes, it is seen as a cognitive tool that can produce behavioural, cognitive, and physiological changes in a participant. For this reason, it is important to ascertain the prevalence and power of placebo when designing an intervention (Evans, 2004). What causes placebo itself is extremely difficult to ascertain, however, three suggested mechanisms recur frequently, and have been shown to accurately predict placebo response, those being:

expectancy, optimism, and susceptibility (Horing et al., 2014; Roseman et al., 2017; Smits et al., 2021; Stewart-Williams & Podd, 2004).

Expectancy can be defined as a prior belief about a treatment. Effectively the literature suggests that if a participant believes in a treatment's efficacy, it will lead to increased performance in and commitment to the tasks they are assigned. Expectancy appears much more often in the psilocybin literature, it is often argued to be a strong moderating variable in response to microdosing regimes (Kaertner et al., 2021). Similarly, it has been shown that expectancy measures can moderate the performance of NF in reducing ADHD symptoms (Lee & Suhr, 2020). In both cases, participants with high expectations of treatment, tend to respond better to said treatment.

As far as optimism is concerned, it appears that it is a dispositional trait. In such, one's general outlook on life itself predicts how likely they are to view an experience as positive or negative. In doing this, a person who ranks highly in optimistic traits may be willing to subjective see a treatment as functioning better, which can lead to objective increases in task performance and in stimulus appraisal (Geers et al., 2010). As a general note, optimism and expectancy are often tied together using the umbrella term "belief" (Evans, 2004).

Finally, susceptibility is the ability of external influences to alter the behaviour of a participant. An example of this, frequently found in science is participant bias, in which a participant's effort during tasks can be modulated by multiple factors outside the self (i.e., environment, experimenter's personality, etc). General manifestations of this phenomenon occur when participants are told frequently about the importance of a study or that a study will be published in an important journal. This in turn leads to them altering how they perform or behave

(McCambridge et al., 2014). In this situation, trait susceptibility moderates how likely participant bias is to occur.

When considering NF, it is important to understand that within most models of NF-based improvement multiple factors are considered. For instance, consideration must be given to NF-based factors (e.g., trainer-participant interaction in a neurotechnology context) but also to nonspecific NF factors (e.g., benefits from generally engaging in an intervention, etc; Ros et al., 2020). Through analysis of placebo response and placebo-controlled trials the goal is to differentiate between these two types of effects, however, they often decussate, making it difficult to ascertain exactly how much of the effect is really being caused by the intervention. Due to this, understanding placebo and even understanding how likely a participant is to respond to a placebo is extremely important for making statements about the efficacy of an intervention.

Current Study

This current study consists of a three-session NF accompanied by two weeks of microdosing. Two distinct groups will be investigated, one group that receives the full intervention and a second passive control group (PCG) who were not exposed to the NF intervention. Both groups will complete an EF test battery. With this, the efficacy of the intervention within and between participants will be examined. In addition to this, placebo response likelihood (PRL) will be evaluated for the experimental group (EXP), these participants will be evaluated on their performance during the EF tasks and NF performance and compared with their likelihood to respond to placebo using measurements of expectancy. susceptibility, and optimism. Specifically, the first hypothesis (H1) is that the EXP will experience more improvement on the cognitive battery (CB) than the PCG. Secondly, it is hypothesised (H2) that

the participants who receive the intervention will illustrate improvement during NF. Finally, it is hypothesized (H3) that the participants who illustrate the most improvement between sessions will score the highest on PRL, in other words, there will be an association between PRL and NF improvement and EF task improvement.

Methodology

Participants

The study consisted of 18 healthy participants (10 male, 8 female), aged between 21 and 37, who were randomly allocated into 2 groups, active (n=10) and passive control (n=8). Participants were sampled from a microdosing workshop conducted by the Dutch Microdosing Institute, to ensure familiarity with psilocybin and ensure safety. In order to ensure the PCG participants remained blinded, during the microdosing workshop it was mentioned that multiple studies were being run at once, this was to ensure that if someone found out that others were receiving NF they did not automatically assume that they were in the control group. Further, participants were screened before joining the study to make sure they passed the following exclusion criteria: (1) They had no history of psychotic mental disorders. (2) They had no family history of psychotic mental disorders. (3) They were not colourblind. (4) They had abstained from drug use for three weeks prior to the first measurement. Participation in this study was voluntary and no rewards were given, however, the truffles used in the study were provided by the Dutch Microdosing Institute, free of charge. Finally, this study was approved by the Ethical Committee Psychology of the University of Groningen and conducted in accordance with the Declaration of Helsinki.

Procedure

Truffles

The participants were supplied with 12g of fresh psilocybe mexicanea truffles. The participants were advised to store the truffles in the fridge or freezer for the duration of the experiment. These truffles were separated into roughly 1g portions. Each portion was expected to contain roughly 1.5mg of psilocybin. The truffles were sold via microdose.nl, the sister-shop of the Dutch Microdosing Institute, participants were supplied with a discount code for participating which when redeemed would remove the cost of the truffles.

Adjustment Window

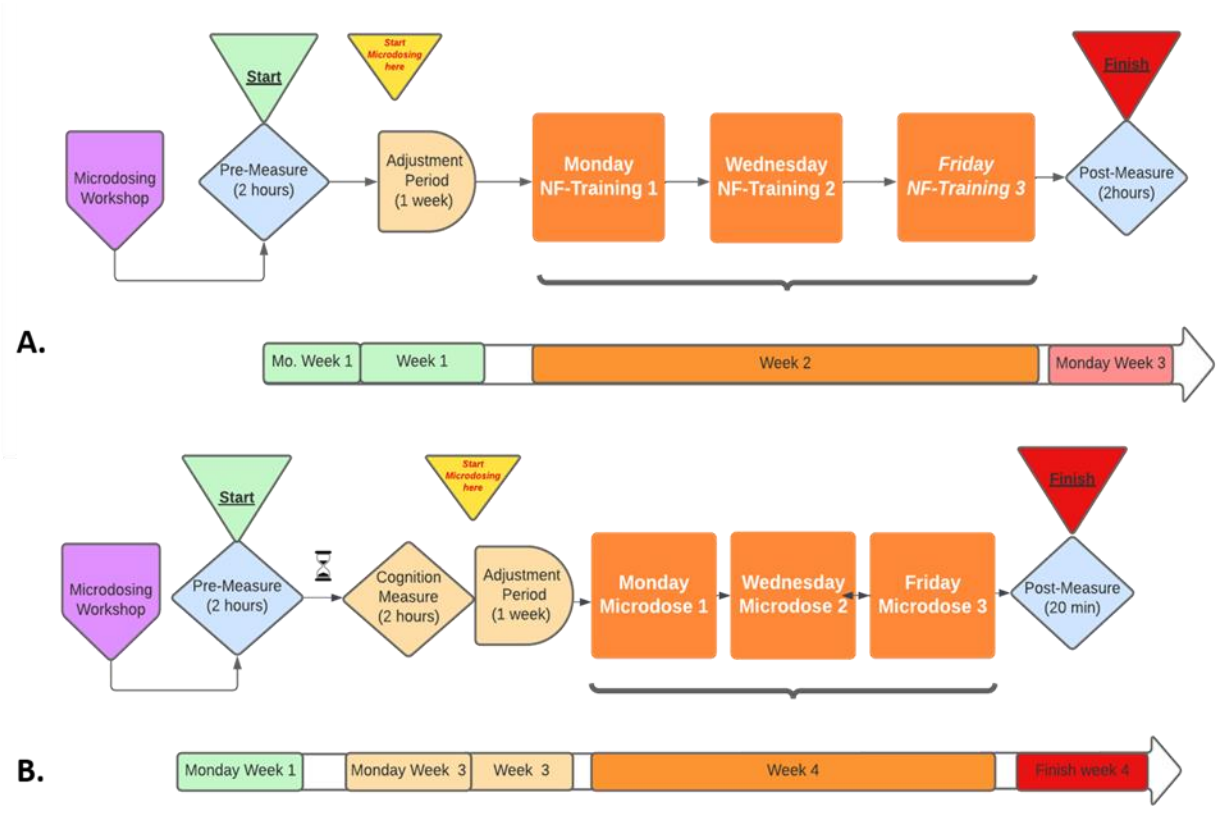
Before beginning the experiment both groups participated in an adjustment window in which the participants attempted to find their "sweet spot" as far as psilocybin dose is concerned. As mentioned above, the truffles come in 1g portions, however, participants were advised to experiment with the dosage during this week and try different dose sizes each day until they become satisfied with their dose. A lower portion limit of 0.5g and an upper limit of 2g was recommended. During the adjustment week, the participants microdosed on Tuesday, Thursday, and Saturday. For the EXP, this adjustment week began the week following their first CB. For the PCG, the adjustment week began the week following their second CB.

Experimental Window

The experimental window followed the week after the adjustment week. For the EXP this consisted of continuing their microdosing regime and attending 3 NF sessions, which lasted approximately 2 hours each. This group was advised to take their dosage of psilocybin as close to two hours before the NF appointment as possible. For the PCG this period did not include the neurofeedback sessions.

Study Design

The first assessment was standardized between groups, this assessment consisted of four cognitive tasks, demographic questionnaires, and placebo questionnaires, taking roughly two hours to complete. Following this assessment, the EXP began the adjustment week followed by the Neurofeedback sessions. During this time the PCG had a two-week break. Following this, both groups again took a similar assessment consisting of the four cognitive tasks and some demographic questions. After this point, the EXP had finished their participation in the study. However, from here, the PCG now began to microdose, firstly with an adjustment week and then followed by a week on a consistent dose. Once this had finished, the PCG then took a final third assessment which collected demographic information once more and provided a reflection survey.



(Figure 1: A) Timetable for EXP. B) Timetable for PCG)

Neurofeedback Protocol

The experimental group received three sessions of NF each separated by one day. During these sessions, they performed five five-minute blocks of NF with three five-minute rest blocks, two at the start and one at the end. The first rest block was used to set an electrooculogram trace, which was used to filter out data containing eye artefacts. Due to the power of eye blinks being so extreme, changes occur across several frequency bands, this becomes problematic as it can lead to artefacts being incorrectly regulated by the participant. For this purpose, electrodes FP1 and FP2 were used and when the artefact-associated frequency was increased to a point that it no longer resembled brain activity, this data was cut out, not allowing the participant to receive feedback for it. The second rest block is used to ascertain the average amount of theta and the final to check once again theta power at rest. The data used for the NF was collected from five electrodes; (Fz, FC1, FC2, Cz, FCz). The aforementioned electrodes fall directly on the FM. To provide feedback to the participant a square was provided in the centre of the screen. The colour and saturation of said box would change depending on the power of theta. If the box went red it indicated that theta had increased relative to the baseline, blue indicated that theta had decreased relative to baseline, and grey indicated no change or an eye blink artefact.

Materials

Executive Functions: Questionnaires, Tasks, and Stimuli

The cognitive assessment consisted of four tasks, these tasks assessed working memory updating, response inhibition, set-shifting, and conflict monitoring. The following tasks were used; the reference-back test, the set-switching task, the stop signal task, and the picture-word interference task. For descriptions of these tasks please refer to Appendix A.

In addition to this, the participants filled out the neuropsychological BRIEF-A survey, a battery that assesses EFs in day-to-day life (Gioia et al., 2018). When filling out this survey the

participants indicate on a three-point scale, marked from “never” to “often”, how well certain behaviours apply to them.

Placebo

Expectancy

Expectancy was split into two categories, pertaining to psilocybin-based expectancy and NF-based expectancy. Psilocybin microdose expectancy was assessed using the adapted scale created by Kaertner and colleagues (2021). This questionnaire exists on a 100-point scale in which the participants rank how confident they are in microdosing and how well they feel microdosing will fit their daily routine. NF-based expectancy was ranked using the Experiences, Attitudes, and Expectations regarding neurofeedback questionnaire. In this analysis, only 2 of the four subscales will be used, those being sections 1 and 2 pertaining to electronic experience and medical technology experience, sections 3 and 4 will not be considered as they are qualitative requiring the participant to reflect upon their own goals. This questionnaire is also scored on a 100-point scale

Susceptibility

Susceptibility was assessed using the Short Susceptibility Survey. It is a shortened version of the Multidimensional Iowa Suggestibility Scale, that specifically focuses on trait susceptibility (Bellman et al., 2004). The questionnaire interrogates how open to suggestion participants are in their day-to-day lives. Generally, it ascertains whether the participant follows trends or is easily influenced by the opinions and arguments of others. This scale was ranked on a 100-point scale.

Optimism

Optimism was assessed using the Revised Life Orientation Task. This is a task that attempts to assess dispositional optimism by asking questions pertaining to the participant's general outlook on life. Each question was ranked on a 100-point scale.

Results

As was previously stated, the intention of this study was twofold; to ascertain the efficacy of the Psilocybin-Assisted NF intervention and to investigate the role of placebo response in the effectiveness of said intervention. Specifically, H1 and H2 stated that those receiving the intervention would experience an improvement in the cognitive tests and in the NF protocol respectively. Furthermore, the H3 stated that those who benefited the most from said intervention would display the highest scores on a PRL scale.

An independent sample's t-test was done to investigate improvement between groups was performed to investigate H1. Improvement between groups was calculated using 2 composite scores of mean reaction time and accuracy during all tasks. Before this test was conducted Levene's test of equality of variances and the Shapiro-Wik normality test were conducted and both assumptions were held. The results of this analysis can be found below in Table 1. There was no difference in the improvement between groups in improvement of accuracy with p=0.839 and effect size d=0.098. When difference in improvement of reaction times between groups was investigated a nonsignificant difference of p=0.180 and a moderate to large effect size of Cohen's d=0.655 was found. Descriptive statistics found a decrease in reaction time of 112.43ms for the EXP and a decrease of -67.39ms for the PCG. In the EXP group, an increase of accuracy of 1.6% was found with an increase of 1.3% in the PCG. A full depiction of the improvements is depicted in Appendix B.

Table 1

Independent Samples T-Test of Reaction Time and Accuracy Improvement Between Groups.

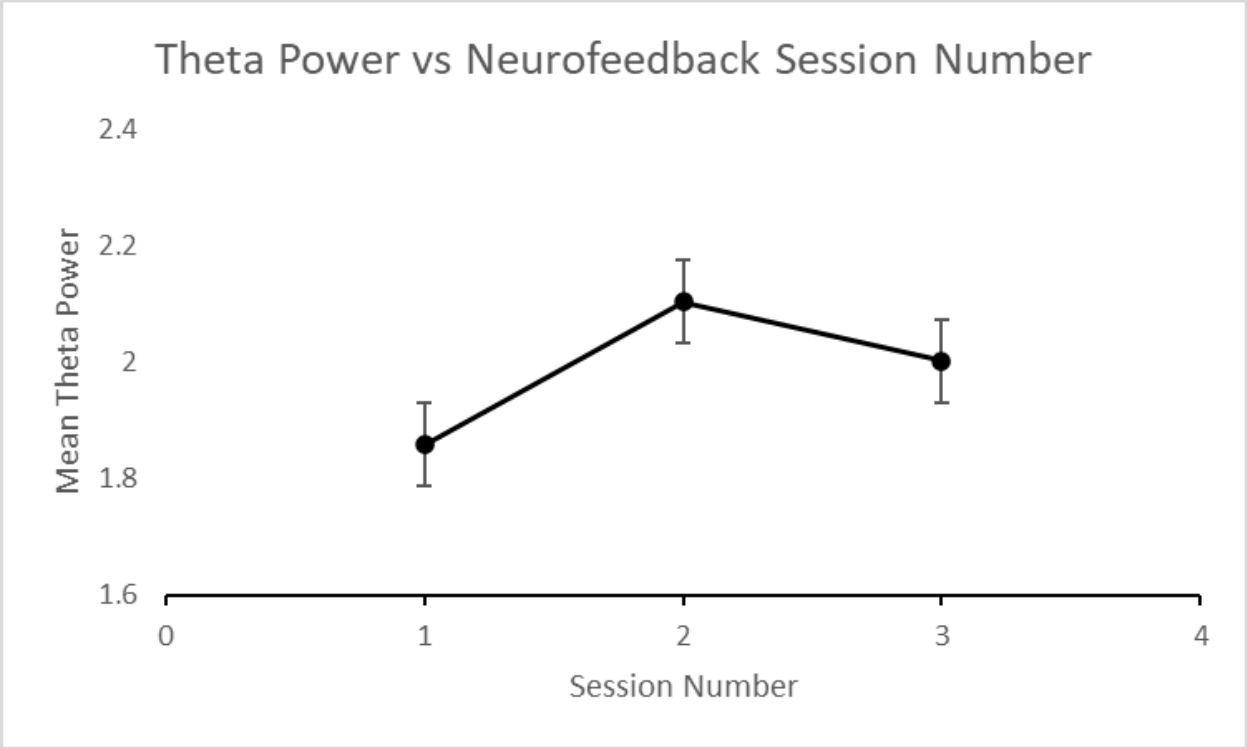
Variable	t	df	p	Cohen's d
Difference Reaction Time	1.401	16	0.180	0.655
Difference Accuracy	0.207	16	0.839	0.098

A repeated measures ANOVA was conducted to investigate H2, the difference within participants between sessions The results of this analysis can be found in Table 2.0. A nonsignificant difference between sessions was recorded p=0.110 with a moderate to large effect size of $\eta 2p$=0.218. Descriptive statistics reported mean theta in session 1 as being 1.858, mean in session 2 as being 2.104, and mean in session 3 as being 2.002. This information can be found in Figure 2.

Table 2

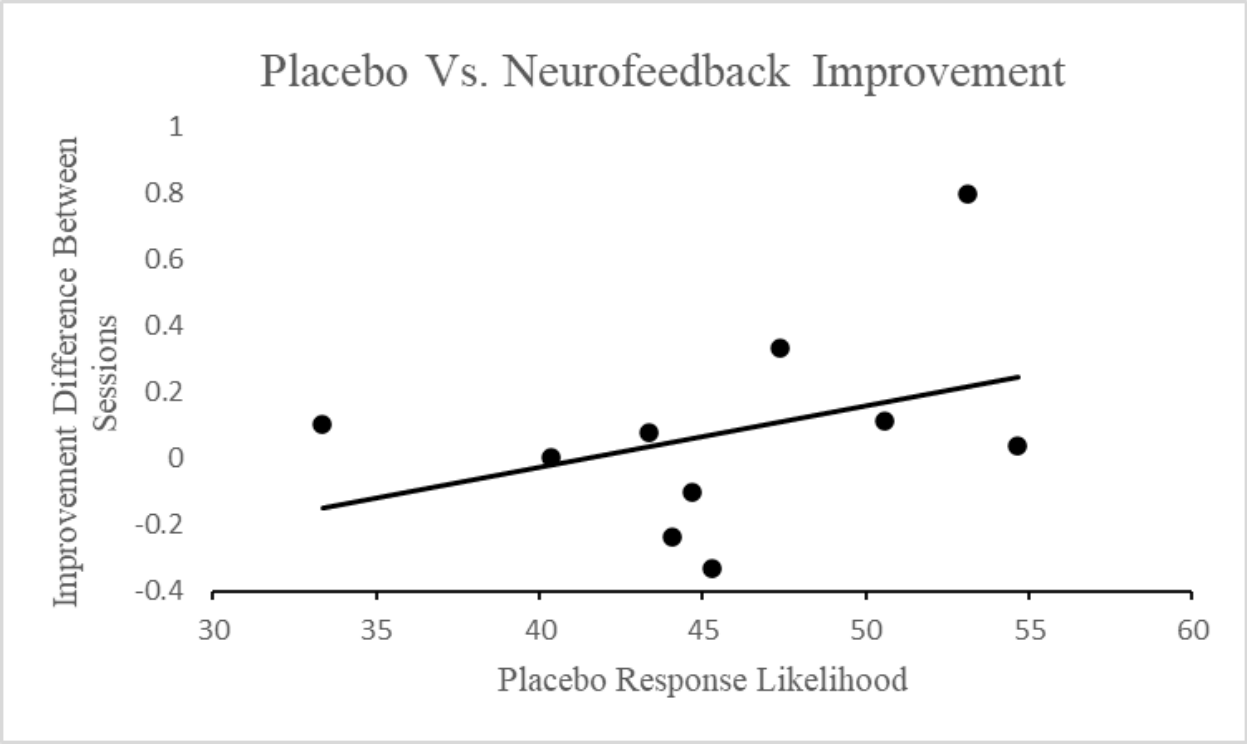
Repeated Measures ANOVA of NF performance between sessions.

Predictor	SS	df	Mean Square	F	p	η2p
Session	0.306	2.00	0.153	2.502	0.110	0.218
Residuals	1.099	18	0.061			



(Figure 2: Theta Power Vs Session Number)

To investigate H3, a correlation between difference in improvement between NF sessions 1 and 3 against PRL was run. To calculate the improvement between sessions, the mean theta from each session had the baseline theta subtracted from it. Then these two values were subtracted from one another. The results of this analysis can be found in Table 2 and can be seen graphed in Figure 3. When this value was correlated with the PRL of each participant a moderate correlation was observed with r=0.370 with p=0.293.



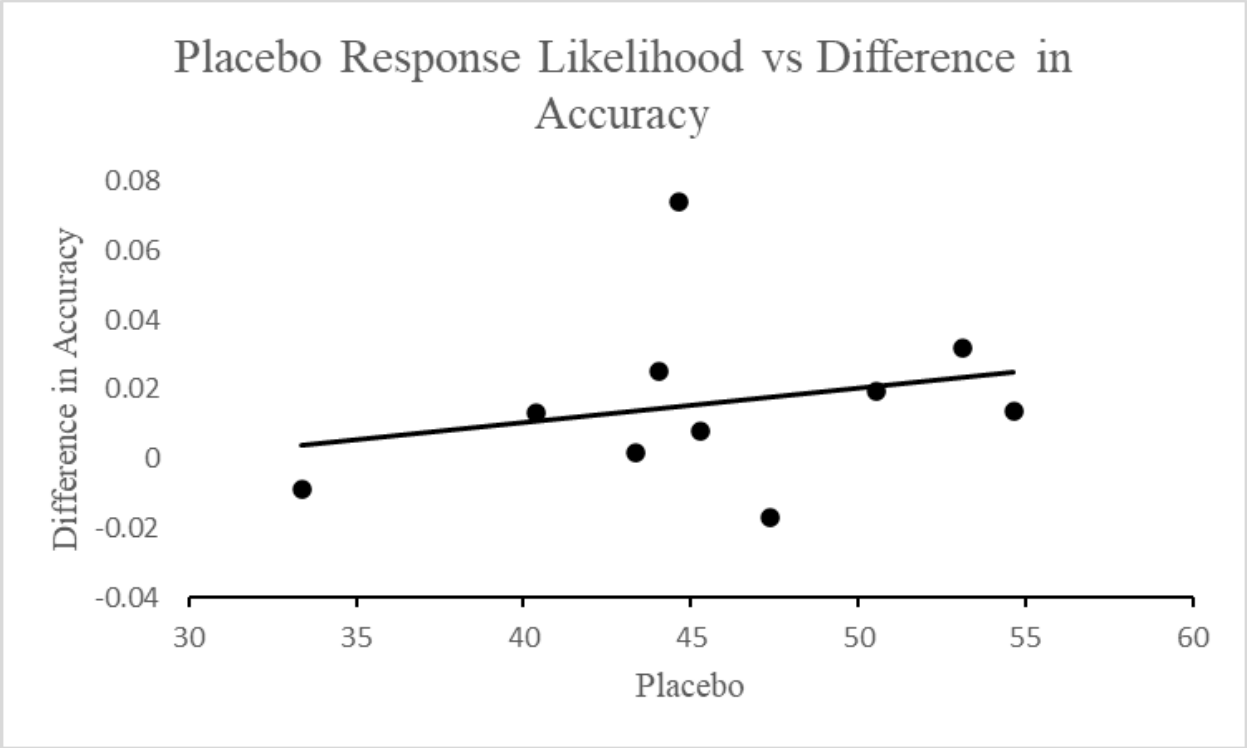
(Figure 3: Correlation between NF improvement and placebo response)

Table 3

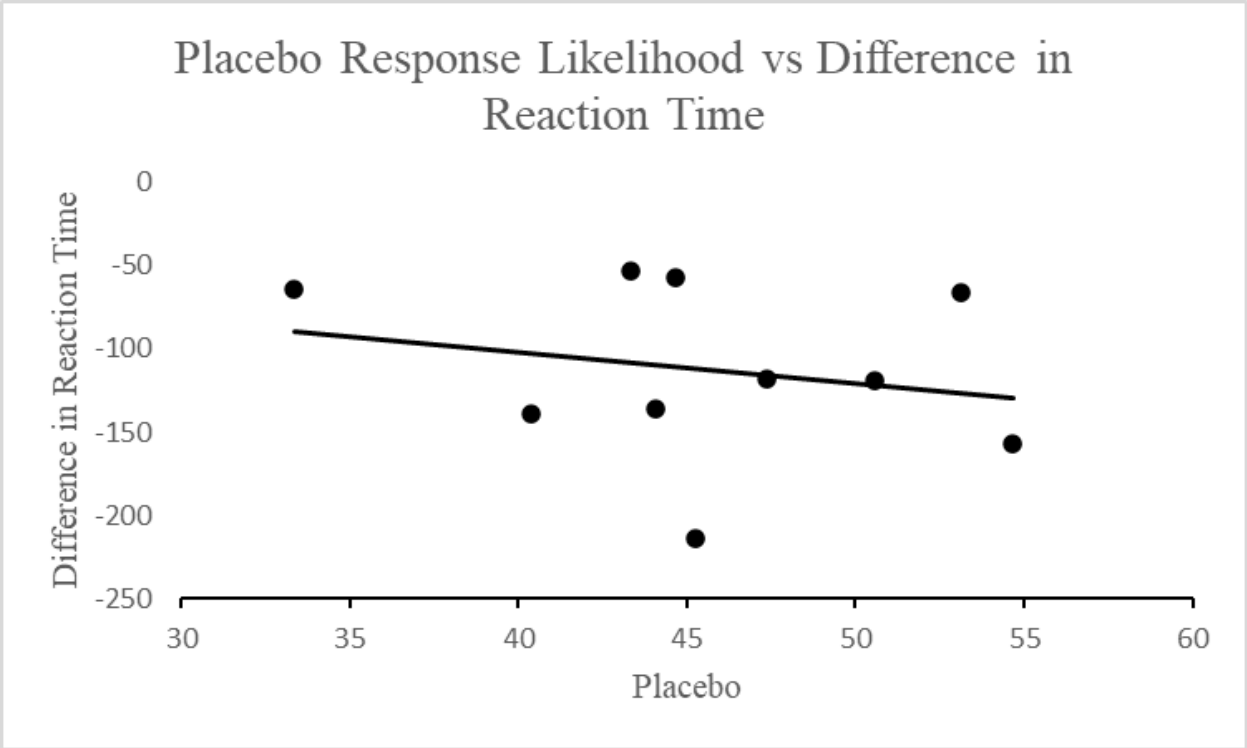
Pearson's Correlation

Variable		Overall Difference	Placebo
Overall Difference	Pearson's R	-	
	P-value	-	
Placebo	Pearson's R	0.370	-
	P-value	0.293	-

Further from this, an investigation of H3 continued with CB and PRL. This was done through a correlational analysis of the composite scores of difference in reaction time and accuracy respectively. Reaction time differences and PRL had a moderate correlation of r=-0.244 with p=0.534. When accuracy differences were considered a moderate correlation of r=0.245 with p=0.496. Graphs of this information can be found below in Figures 4 and 5.



(Figure 4: Correlation between Placebo and Difference in Accuracy)



(Figure 5: Correlation between Placebo and Difference in Reaction Time)

Discussion

This study had two overarching goals; 1) to investigate the novel protocol of psilocybin-assisted NF and 2) to evaluate the role of placebo in combining microdosing and psilocybin. This was done through evaluation of two groups, one group that received the entire intervention and a PCG who received no intervention.

To begin interpreting the results, it is important to stress one caveat, the sample size for the EXP fell short of what was expected due to this, all tests will likely present without statistical significance due to an absence of adequate power, for this reason, interpretation primarily of effect sizes, correlation values, and consideration of clinical significance will follow.

Firstly, Considering H1, that the EXP would see more improvement than the PCG. This hypothesis is strongly supported in regard to reaction time; however, little evidence illustrates support that increased improvement could be seen in accuracy. This in turn means that H1 only partially holds, as from the outset it was expected that accuracy would have seen significant improvement also. It is hard to make an inference as to why this would happen when the difference between groups in reaction time is so large. However, it is likely that this effect is not caused by psilocybin or neurofeedback and is more than likely caused by experimental factors. When the data is examined qualitatively almost none of the participants improved between sessions, this may be due to the EF tasks not being sensitive enough and creating a ceiling effect or it is also possible that the use of a composite score may lead to this. Assuming that an across-the-board improvement in accuracy follows the intervention partially misrepresents the tasks. All of the tasks have certain components which involve EFs, however, certain parts do not. For example, in the memory updating task, conditions in which a new reference is set are more

challenging and it is possible that in these situations the intervention may have yielded an improvement in accuracy and such by using a crude holistic measure, it is possible that differences like this are missed.

Secondly, to consider H2, that EXP would experience an improvement throughout the NF protocol. The effect size was promising given the sample size. However, two issues appear when the data is examined, the first being that most participants improved more in session 2 than session 3, this is not what was expected, as NF is considered to be a learning-based intervention (Autenrieth et al., 2020). This likely was caused/moderated by the second issue, which is the actual gains made by the participants. Although participants illustrated some improvement, a lot of the increases in theta were small, with some participants having very high baselines. This may be due to the fact that the psilocybin dose and the neurofeedback occurred on the same day leading to acute changes in neuronal connectivity and neuronal blood flow. Blood flow changes are commonly reported during macrodoses of psilocybin. Carhart-Harris and colleagues (2012) investigated the neural correlates of psilocybin while under a fMRI scan. They found that there was a sharp decrease (up to 30%) in blood flow in the thalamic and cingulate areas. Cerebral blood flow has been illustrated to have influence on performance of EF tests with decreased cingulate blood flow being indicative of a decrease of rumination, memory impairment, and executive dysfunction in depressed patients (Carhart-Harris et al., 2012; Liao et al., 2017); Tari et al., 2020). This could have led to the upregulated baseline theta.

Furthermore, alterations in network connectivity during psilocybin use are common. Specifically, the CEN, modulates EFs, with connectivity of this network being vital for the adequate performance of tasks requiring EFs (Haut et al., 2017). The DMN has also shown to be implicated in executive functioning, although the primary goal of the DMN is resting-state self-

referential tasks, during engagement of a challenging task, a task-induced deactivation occurs. It is hypothesized that this task-induced deactivation occurs to “free up space” for the CEN and facilitate cognitive functioning (Brown, 2017). When we consider this information in conjunction with the fact that psilocybin use leads to increased internetwork connectivity and decreased modularity, it is possible that psilocybin could disrupt this coupling. Due to this, the dose of psilocybin may have implications for NF performance or even directly influence theta power.

Finally, with regards to H3, it was hypothesized the placebo scores would correlate with the NF improvement and the improvement between cognitive batteries. With regard to the NF improvement a moderate to strong correlation between both scores was found. This is in line with what was hypothesized suggesting that those who benefit the most from NF are also most likely to respond to a placebo. One possibility for why these two are strongly related is due to the fact that we used the same factors to operationalise them. As mentioned earlier, susceptibility, optimism, and expectations are used to predict placebo response, but they are also implicated in response to NF, meaning it is possible that response to NF or placebo may be moderated by similar mechanisms. This becomes even more challenging to interpret when you consider the role of psilocybin. Psilocybin increases optimism and suggestibility (Rucker et al., 2022), which means it is rationale to assume that these factors will be altered through use of this drug, which in turn could lead to moderation of placebo or neurofeedback response or both. This overlap of mechanisms makes it worth considering neuroenchantment. Neuroenchanment postulates that by creating the correct environment a placebo response can be attenuated and become extremely strong. Generally, this response is referred to as a “superplacebo”. when considered in tandem with the specific and nonspecific effects of a neurofeedback intervention (Ros et al., 2020), it is

possible that the introduction of psilocybin into a NF environment attenuates these nonspecific effects. For instance, patient expectancy is often higher when participants are assigned pharmaceutical interventions (Laferton et al., 2018). This, in turn, could strengthen the placebo response factor already assumed to be considered in NF, in a mechanism similar to the creation of superplacebo through environmental modification (Olson et al., 2021), which could possibly lead to improved performance in the NF regardless of functionality of the previously touted neuroplasticity hypotehsis. Effectively, what is important to understand is that due to the many avenues in which psilocybin can affect the NF set-up it is difficult to ascertain whether we can attribute any NF improvement to specific or nonspecific factors.

To continue considering H3, when comparing the placebo scores with the improvement across the CB. Both reaction time and accuracy improvement correlated moderately with PRL. This is in line with what was hypothesized and in combination with the neurofeedback and placebo results provides a strong argument that PRL may be implicated in the mechanisms of NF promoting EF. However, this being said, one thing that is interesting is the difference between NF improvement and either of the CB improvements, with NF seeing a slightly stronger correlation to PRL. This may occur because NF is extremely sensitive to environmental factors (Marzbani et al., 2016). The placebo scale was predominantly designed to identify placebo responses moderated by environmental and social modification so this could moderate the slightly stronger correlation. Further when it is considered that the CB measures were delivered online and the neurofeedback in person, it to an extent makes sense why those who are more sensitive to placebo performed more in line with expectation than in during the CB.

Study Limitations and Future Research Directions

One issue with the study protocol was the sampling method used. Participants were sampled from a workshop on the topic of psychedelics and then randomised into groups. In order for the participants to be included in the study they had to have indicated independent interest in microdosing, this creates two problems, these people who are partaking in the experiment likely have strong expectations with ulterior motives compared to a regular randomised controlled trial. From qualitative analysis of the demographic questionnaires, the participants indicated more experience with psychedelic drugs than would be expected from a normal population (92% participants indicating previous psychedelic use). Both of these circumstances could upregulate expectation and therefore placebo appearance (Evans, 2004) .

A further issue occurred due to the experimental structure; the participants were allowed to begin the study across 7 weeks. However, the PCG and EXP experimental lengths differed meaning that for the final two weeks, they could exclusively be placed in the PCG. This timing issue also created somewhat of an attrition effect, meaning that although an attempt to pre-empt participants dropping out was made, when EXP participants dropped out after week 4 it was impossible to find a suitable replacement in time to take their spot, leading to a sample size that was less than desired.

With this being said, both of these limitations are a product of the fact that this trial was a pilot study, both of these issues will be resolved in the full trial. However, one thing important to highlight is the difference between PRL and placebo response, without a doubt the next step for research in psilocybin-assisted NF is doing a fully placebo-controlled trial, however, in my opinion, the introduction of a placebo group should not be in lieu of a PRL scale. By making an effort to screen participants for how likely they are to respond to placebo we can continue to investigate the link between the mechanisms behind neurofeedback and placebo and the nature in

which they overlap. For this reason, it would be favourable to not only conduct PRL research in place of placebo but also with it.

Study Strengths

The study was the first to integrate NF and psilocybin, this is an important step in addressing the large proportion of people who are Brain-Computer Interface (BCI) illiterate. Usually, attempts are made to address this illiteracy by focusing on improving the training protocols given to participants (Autenrieth et al., 2020) or by trying to improve the classifiers used by BCIs (Vidaurre & Blankertz, 2010). However, this study could function as a step towards a pharmaceutical approach to targeting BCI response.

Conclusion

The introduction of psilocybin to NF has shown effects in the correct direction when it comes to moderating NF performance and has shown moderate to strong improvement in cognitive batteries assessing EF. This being, it is an intervention with many moving parts and may be moderated by placebo. For this reason, more research is required to identify the strength of this treatment protocol and to understand the mechanisms involved in this intervention.

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Appendix A

Conflict Monitoring

Conflict monitoring, also known as the picture-word interference task, which is based on the well-known Stroop task, the participants were exposed to congruent and incongruent conditions, in which a stimulus and a word were presented to them. During the task, based on the colour of the frame surrounding the image, they had to either categorize the word or image into land or sea animal categories, this was done by using the “X” and “M " buttons on the keyboard. The task consisted of 140 trials divided into 4 blocks with short breaks between each block, of which the congruent and incongruent trials appeared an equal number of times. Before these 140 trials, 3 practice trials occurred. Each trial began with a fixation-cross presentation which lasted between 300ms and 600ms followed by the aforementioned stimuli for 2600ms. If participants responded before the stimulus presentation the trial would be voided and the border go grey.

Task Switching

The task switching task is based on the principle of the Wisconsin card sorting task. In this task, participants are presented with images of animals (land and sea) and strings of letters (upper and lower case). The colour of the border indicates what the participant should sort, animal type or letter case, the participant uses “X” and “M" to do this. This task consisted of 172 trials, the first 32 trials served as a baseline in which the conditions do not switch, and the final 140 trials switch between conditions frequently (4:6 ratio of switch vs no switch) and are separated into 4 blocks each with a short block between them. The trial structure is the same as the task above with a fixation-cross presentation between 300ms and 600ms and stimulus presentation up to 2600ms following this.

Inhibition

The inhibition task, or stop signal task is another form of adapted Stroop test, in which participants have to categorize present pictures into categories of land or sea animals. Participants used the “X” and “M” keys to categorise. In some trials, participants were presented with a “stop” signal, by changing the colour of the border. To balance the stop signal, two different coloured borders were used indicating no The presentation of this stop signal is delayed on a moving scale, which means depending on the accuracy of the participant's response the warning given before the stop trial changes. This was done in an effort to keep the success rate of the trials around 50%. The trial structure is the same as the task above with a fixation-cross presentation between 300ms and 600ms and stimulus presentation up to 2600ms following this. The stop signal delay had a length of 250ms with every response altering it by plus or minus 50ms based on if the response was correct or not, the delay reset to 250ms if a threshold of 90ms or 910ms was crossed. This task consisted of 400 trials split across 8 blocks.

Memory Updating

The memory updating task is based on the principles of the reference-back task, in which two reference and comparison trials occur. Participants are displayed pictures of animals, land and sea, and must indicate whether their category matches that of the reference. The reference is indicated by a change in border colour and changed throughout the trial. The participants indicate congruence or incongruence using “X” and “M" buttons on their keyboard. The task consisted of 240 trials divided between 4 blocks with short breaks between each block. Trials using land and sea animals as references are made equal, however, reference trials occur less often than comparison trials with a ratio of 1:3, further, a reference trial cannot follow a reference trial and there can be no more than 5 comparison trials following one reference. The

trial structure is the same as the task above with a fixation-cross presentation between 300ms and 600ms and stimulus presentation up to 2600ms following this

Appendix B

Table 4

Session 1 Descriptive Statistics of Cognitive Battery

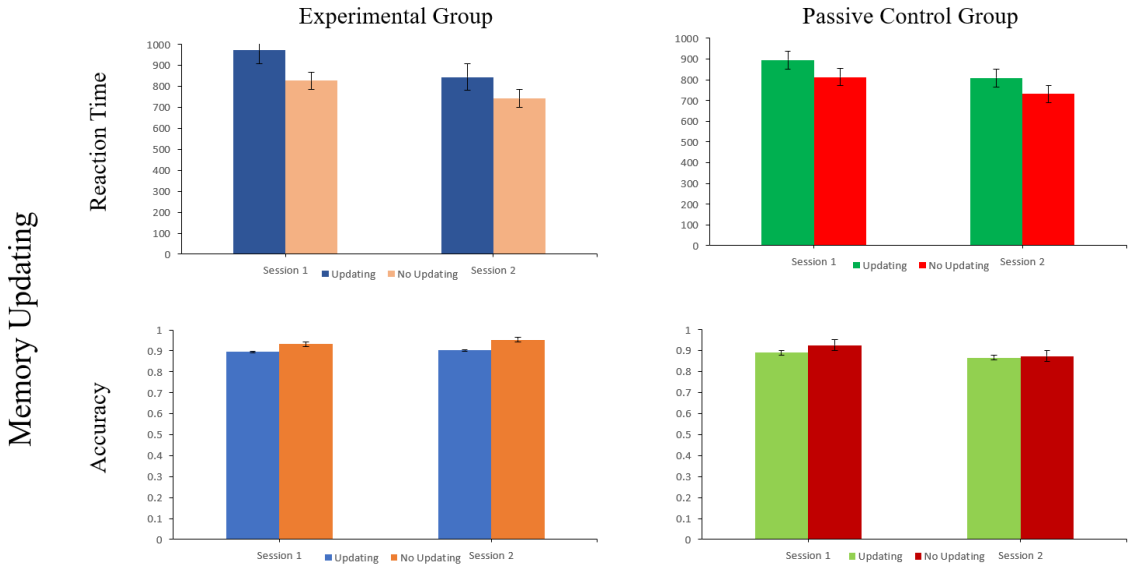
Group			PCG	EXP
RTs	CM	*Conflict*	1310,93	1415,32
		No Conflict	1150,39	1223,47
	MU	*Updating*	894,85	971,70
		No Updating	812,90	826,27
	IN	*Go*	791,93	726,96
		Stop	330,20	264,35
	TS	*Repeat*	870,84	902,07
		Switch	1079,08	1175,29
Acc	CM	*Conflict*	0,66	0,72
		No Conflict	0,85	0,87
	MU	*Updating*	0,89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

Table 5

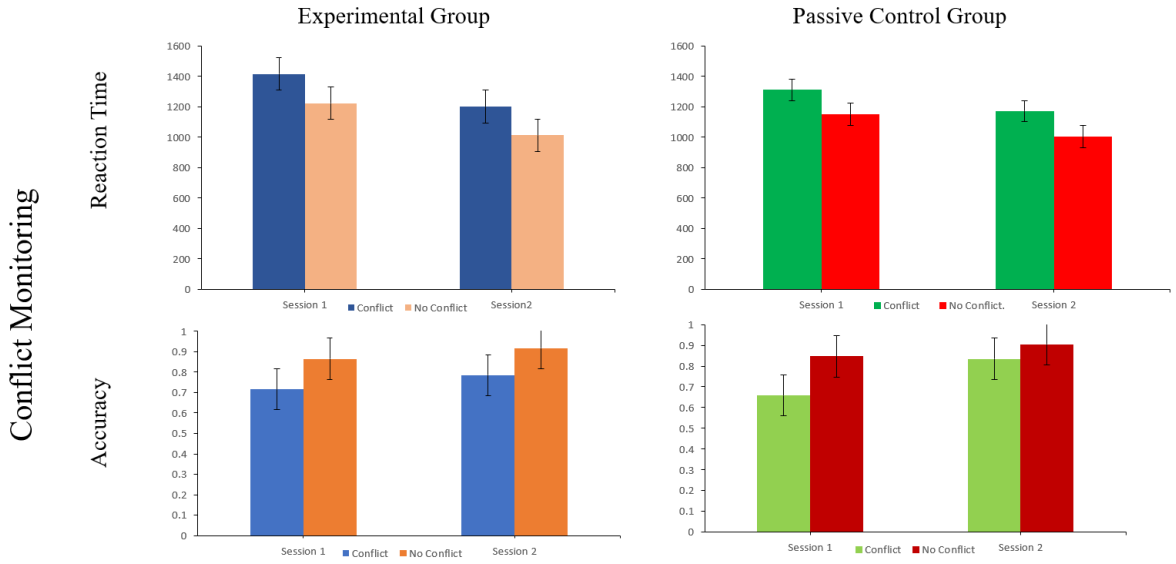
Session 2 Descriptive Statistics of Cognitive Battery

Group			PCG	EXP
RTs	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

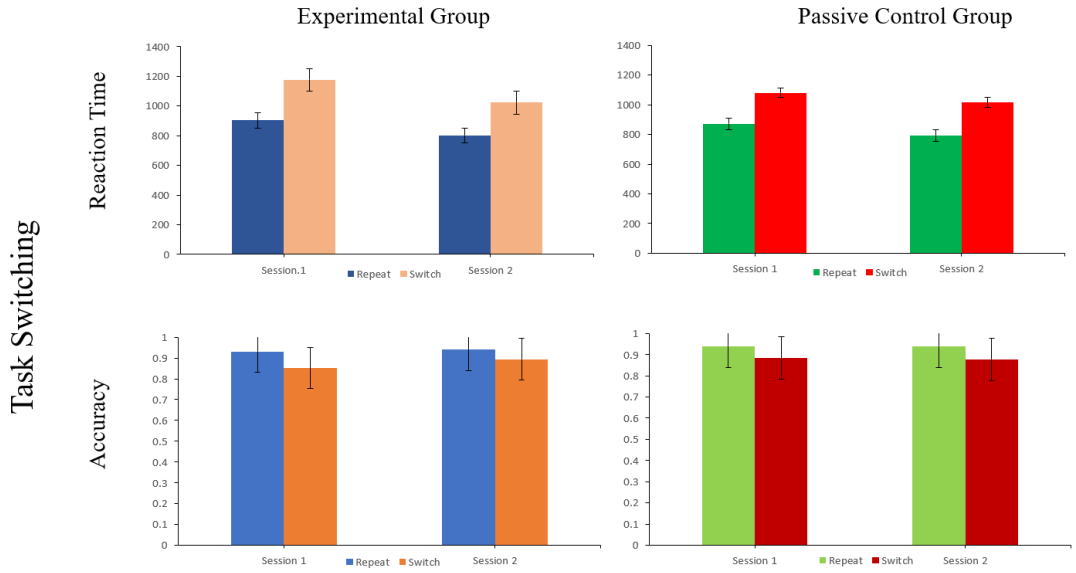
Acc	CM	*Conflict*	0,83	0,78
		No Conflict	0,90	0,92
	MU	*Updating*	0,87	0,90
		No Updating	0,87	0,95
	IN			
	TS	*Repeat*	0,94	0,94
		Switch	0,88	0,89



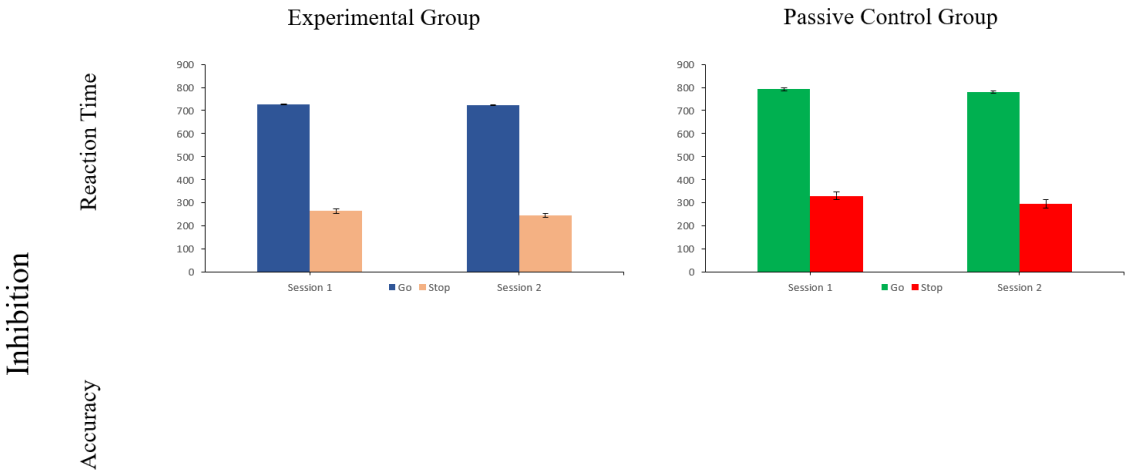
(Figure 6: Memory Updating Graphs between Sessions for Reaction Time and Accuracy)



(Figure 7: Conflict Monitoring Graphs between Sessions for Reaction Time and Accuracy)



(Figure 8: Task Switching Graphs between Sessions for Reaction Time and Accuracy)



(Figure 9: Inhibition Graphs between Sessions for Reaction Time)