PLACEBO EFFECT AFFECTING ATTENTION - A Smart Pill

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Objective: This research study attempted to establish the effect of placebo on attention.

Methods: Study participants were 38 students from the University of Zagreb, age 20 to 27. Before the Evoked Related Potential (ERP) measurements, the participants either took or did not take the „Brain Improver" placebo pill, depending on the experimental condition to which they were exposed. A Stroop test constructed for the purposes of this research study was used for testing selective attention.

Results: The placebo effect was obtained as an ERP effect on P2 and N2 components that reflect attentional processes as well as classification processes related to the Stroop stimuli.

Conclusions: The results suggest that the placebo effect is a significant modulator of attention; therefore it is important to further study its effects not only in clinical or pharmaceutical trials but also its impact on the entire range of cognitive functions in general populations.

Keywords: Placebo effect, attention, evoked related potentials (ERP)

1. Introduction

The placebo effect has been one of the most investigated constructs in psychology and medicine in the last 50 years; hence numerous definitions describe it as a reaction to treatment or medication. However, placebo can also refer to different stimuli like music, pictures, and symbols. We can therefore define it not as treatment alone, but as an event within a set of sensory and social stimuli that indicates to an individual that a beneficial intervention is being administered (Benedetti, 2014). Placebo effect has been studied not only with instruments of psychological assessment, which are often self-reported and subjective, but also with brain imaging technology, which is objective. Many positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies related to the placebo effect have examined primarily its psychophysiological aspect (see review: Jubb & Bensing, 2013). Meanwhile, the psychological segment that is associated with expectations and beliefs is much more complex to explore, even with the most sophisticated technology.

The first positron emission tomography studies (Petrovic, Kalso, Petersson, & Ingvar, 2002) already demonstrated increases in regional cerebral blood flow as the response of μ-opioid receptor system in the rostral anterior cingulate cortex as a function of placebo response with expectation of analgesia(Sovilj, Kovic, Biros, et al., 2014). However, fMRI studies showed placebo effects as a result of activities in the orbitofrontal and dorsolateral prefrontal cortex during the anticipatory phase which preceded reductions in the activity of pain-responsive regions when subjects were submitted to a painful heat stimulus (Wager et al., 2006). Studies of directing and distracting attention in relation to painful stimuli additionally confirm the relevance of expectations and placebo effect in persons enduring pain. In a pain and placebo study, Wager, Matre, and Casey (2006) showed that placebo treatment produced a significant decrease in P2 amplitude and that P2 placebo responses were large enough to reflect a meaningful difference in nociceptive processing. According to Wager and colleagues, one of the main characteristics of placebo is that it can induce an affective/motivational state which leads to reduced attention to pain.

In addition to the importance of studying what is among the best known phenomena in psychology, the relevance of this line of research comes from its connections with and contributions to the understanding of neurological diseases and disorders. For example, placebo response in Parkinson's disease is associated with a release of endogenous dopamine in the striatum (de la Fuente-Fernandez et al., 2001) or reduced activity in single neurons of the subthalamic nucleus (Benedetti et al., 2004; for a review see Beauregard, 2007). This could potentially indicate that the psychological effect of expectations plays an important role in placebo effect in patients with neurological disorders as well.

Having in mind that placebo effect is associated with expectancy; many studies have begun to investigate the effects of placebo on physical performance, cognitive functions (especially memory), perception, attention, executive functions, and experience of pain. Previous studies have suggested that placebo could increase physical performance (Beedie & Foad, 2009; Pollo, Carlino & Benedetti, 2011) which raises important questions as to how these effects should be exploited in competitive sports. There is evidence that placebo and expectations can improve cognitive performance as well (Oken et al., 2008, Parker et al., 2011). Expectancy effect producing improvements in cognitive functions has been studied primarily in trials involving stimulants such as caffeine (Oken et al., 2008). Expectancy of stimulant administration may cause improvements in reaction time and mood states (Mitchell, Laurent, & de Wit, 1996). The neurobiological mechanism of expectancy effects shows that expectancy is related to specific neurotransmitter systems and specific cerebral localizations in placebo analgesia (Amanzio & Benedetti, 1999; Zubieta et al., 2005).

While the placebo effect is one of the most vigorously researched constructs in psychology, neuropsychology, pharmaceutical trials, pain research, and related fields, previous research has produced mixed findings about the exact nature of the relationship between placebo effects and cognitive functions. Eskridge (1975) studied the effect of placebo on reaction time in a visual perception tasks and obtained no significant differences between the placebo condition (sugar pill) and a control condition (no pill). Contrary to these findings, Fillmore and Vogel-Sprott (1992) studied the influence of caffeine on a motor-functioning task with a group of participants receiving placebo and found a significant placebo effect. In a study of using the Stroop task, George and associates (2004) found hemispheric differences attributed to placebo effect during the response choice and functional connections of left midcingular region with left insula and temporal and frontal cortex during cognitive interference. Other studies related to placebo and cognition show improvements on tasks related to

perceptive speed (Anderson & Horne, 2008; Colagiuri, Livesey, & Harris, 2011). Green (2001) used a balanced placebo design in which he found that glucose administration enhanced recognition memory times and performance on a vigilance task only in sessions when subjects were informed about receiving glucose and not when they were told that they would receive aspartame. Oken et al. (2008) found significant effects of pill-taking on a word-list delayed recall task and on a Stroop color-word task. However, very little is known about the biological underpinnings of these cognition-enhancing effects of placebos.

Many neuroimaging studies have showed that beliefs and expectations play a pivotal role in placebo (Shapiro & Shapiro, 1997; Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005; Amanzio & Benedetti, 1999; Breiter, Aharon, Kahneman, Dale & Shizgal, 2001; de la Fuente-Fernandez et al., 2001). Yet, only a small number of studies use the Evoked Related Potentials (ERP) technique in investigating the placebo effect. Reasons probably lie in the fact that ERP is less illustrative in pinpointing the neurobiological mechanisms of pain, analgesia, and placebo. The purpose of the present study was to investigate the role of placebo in cognitive functions using the Electroencephalography/Evoked Related Potentials (EEG/ERP) technique in order to detect an objectively measurable change in neural (cortical) activity related to the presence of the placebo agent (*Brain Improving Pill*). We attempted to show the effect of the consumption of a "Brain Improving Pill" on attentional processing, more specifically, reaction time, by using a Stroop task. Unique contributions of our study are: a) strengthening of the theory of placebo by detecting real changes in neuronal activity, b) demonstrating the presence of the placebo effect in fields other than neurological disorders, and c) adding evidence for the significance of placebo on attentional processing.

2. Participants

Participants in the study were 38 undergraduate and graduate students (18 women, 20 men) from the University of Zagreb. Average age was 21 (M = 21.03, sd = 1.10). Average score on the Edinburgh Handedness Inventory Questionnaire that examines dominance of the left or right hand in daily activities shows that all participants were right handed. Average score on Raven Progressive Matrices, a non-verbally based measure of intelligence, was 118 (M = 118, sd = 2.74). All subjects were informed about the nature of the experimental procedures which they would undergo prior to recruitment. Potential participants who were left handed, had lower-than-average IQ scores, a history of brain injuries, a history of diabetes, and/or were currently dieting to lose weight were excluded from participating in the study.

Table 1: Descriptives

	Male	Female
N	18	20
Age (M, sd)	21.03, 1.10	24.8, 3.8
Years of education (M, sd)	14.7, 2.8	14.5, 2.1
Raven Matrices (score) (M, sd)	129.3, 12.1	127.6, 13.5

3. Methods

3.1 Procedure

The study was carried out in the Laboratory for Psycholinguistic Research at the University of Zagreb between January and May, 2014. The study was approved by the Zagreb University Research Ethics Committee and all participants gave informed consent prior to participating. There were no financial nor any other benefits for the participants.

After the Raven Matrices measure of intelligence was administered, the selected participants were randomly divided into two even-sized groups of 19 participants. The groups served a purely administrative function for the sake of tracking the study design and proper placebo-no placebo administration and assessment; the participants completed the Stroop task individually. Each participant's performance was assessed two times: once with the administration of the placebo and once without. The placebo was a red sugar-pill named the *Brain Improving Pill*. Participants were told that the *Brain Improving Pill* improved cognitive functioning, attention, and concentration. There was a time lag of two to three weeks between the two assessments for each participant. Participants in Group A first performed the Stroop task without having taken the Brain Improving Pill and had the Brain Improving Pill administered at the beginning of the second assessment. Meanwhile participants in Group B received the Smart Pill at the time of the first assessment and had no placebo at the time of the second assessment. These repeated-measures experimental design strengthened the conclusions we would draw based on the obtained results.

Participants' cortical activity was measured through electroencelography (EEG). Participants were instructed to sit in front of a computer screen (size: 48x30 cm, Samsung SynMster T220) at a distance of 1 m. Brain Products Recorder (Brain Products GmbH, Munich, Germany) was used for recording EEG signal from the QuickAmp128 amplifier (Brain Products GmbH, Munich, Germany). The 32 channel actiCAP (Brain Products GmbH, Munich, Germany) was used with the electrodes arranged according to the 10 - 10 system. The continuous EEG signal was sampled with 1 kHz. Eye movements were recorded on two bipolar electrodes (HEOG, VEOG). Brain Products Vision Analyser software was used for off-line signal analysis.

Correction of ocular artefacts was applied to all 32 EEG channels based on the Gratton and Coles's algorithm for each EEG channel. After artefact correction and low pass filtering (30 Hz), the recorded signal was segmented into 1100 ms long segments (from -100 ms to 1000 ms after the stimulus onset). The segmented data were averaged and the mean amplitude values were calculated for the relevant time windows for each participant. The numerical data were exported for statistical analysis.

After being prepared for the EEG recording, participants started working on the Stroop task.

3.2 Instruments

Stroop task

We constructed a Stroop task specifically for the purposes of this study with the aim of measuring selective attention. Our Stroop task was modified for Croatian language according to the model presented by Roelofs & Lamers (2007). The original Stroop task consists of pictures of colours with congruent or incongruent colour names printed inside the picture, while we used images of objects and animals. The task consisted of a total of 180 pictures of animals and objects in different combinations with text written inside each picture. More precisely, there were 30 black-and-white pictures of animals and 30 pictures of objects. Inside each picture was text that was congruent, incongruent or neutral in relation to the image shown. For example, the image of a cat had the word "*cat*" (Croatian - macka) written in it in the congruent condition, the word "*chair*" (Croatian - stolac) in the incongruent condition, and finally had neutral content like "*xxxx*" in the neutral condition. During the selection of animals and objects, we took care to choose those whose names in Croatian had two syllables. In other words, we ensured that the words were equal in length and frequency, so that they would take up the same space in participants' phonological memory while they worked on the task. Total duration of the task was 10 minutes. The task was programmed using the E-prime stimulus presentation software **(**Schneider, Eschman & Zuccolotto, 2002). The Stroop task requires the participant to inhibit reactions to the text and to respond only to the image by pressing the corresponding button (congruent, incongruent, or neutral) on the response box. Results

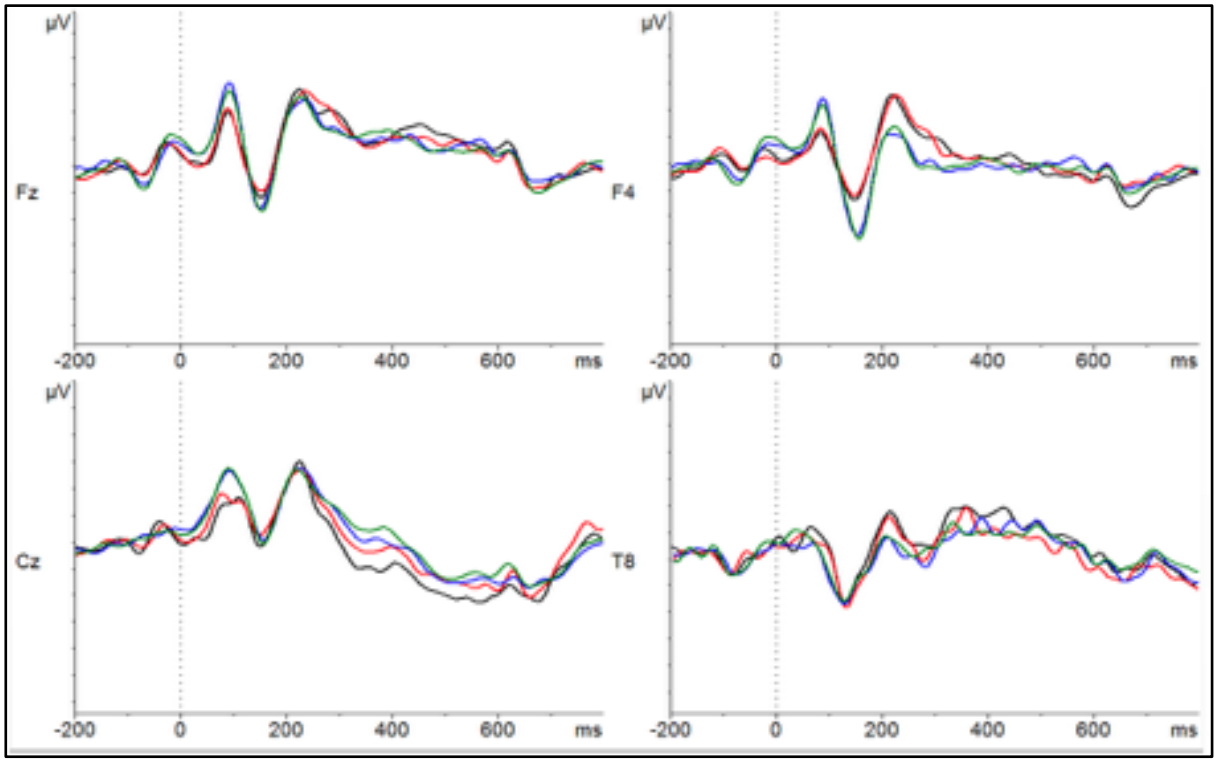
on the test indicate the number of correct and incorrect responses as well as total reaction time to a given stimulus.

4. Statistics

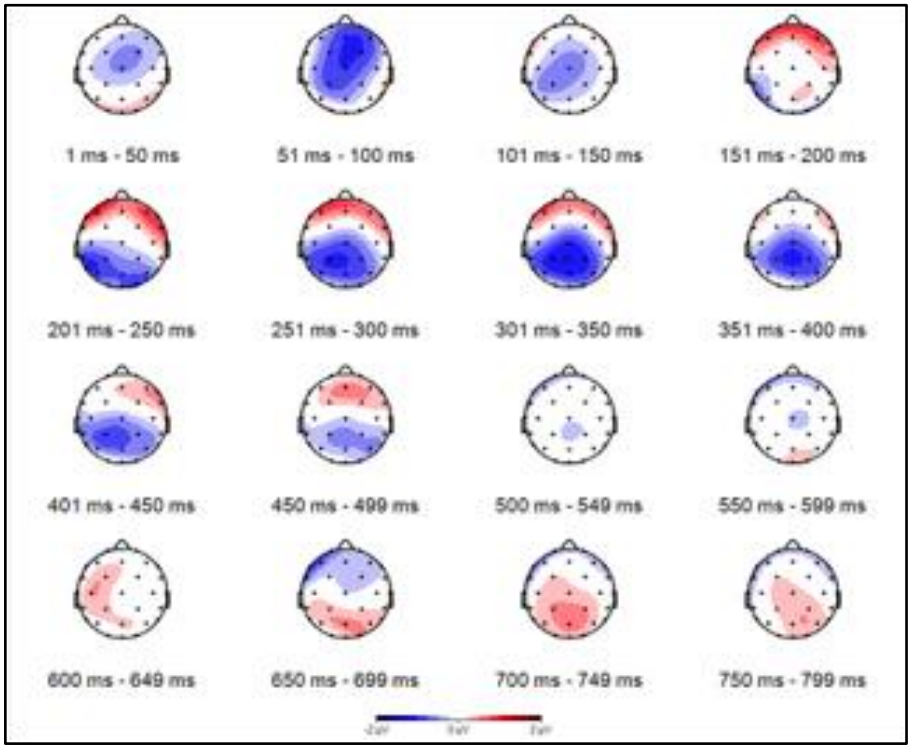
Data were analyzed using SPSS (SPSS IBM Version 21, Polar Engineering and Consulting). Generalized linear model (GLM) for repeated measures was used to calculate the difference in activity of the frontal cortex in two conditions. Using the Bonferroni post hoc test, differences in activities of the left and right hemispheres between individual conditions and electrodes were analysed. Considering that data did not meet the criteria of sphericity, Greenhouse-Geisser correction of degrees of freedom was calculated and used for analysing the results.

5. Results

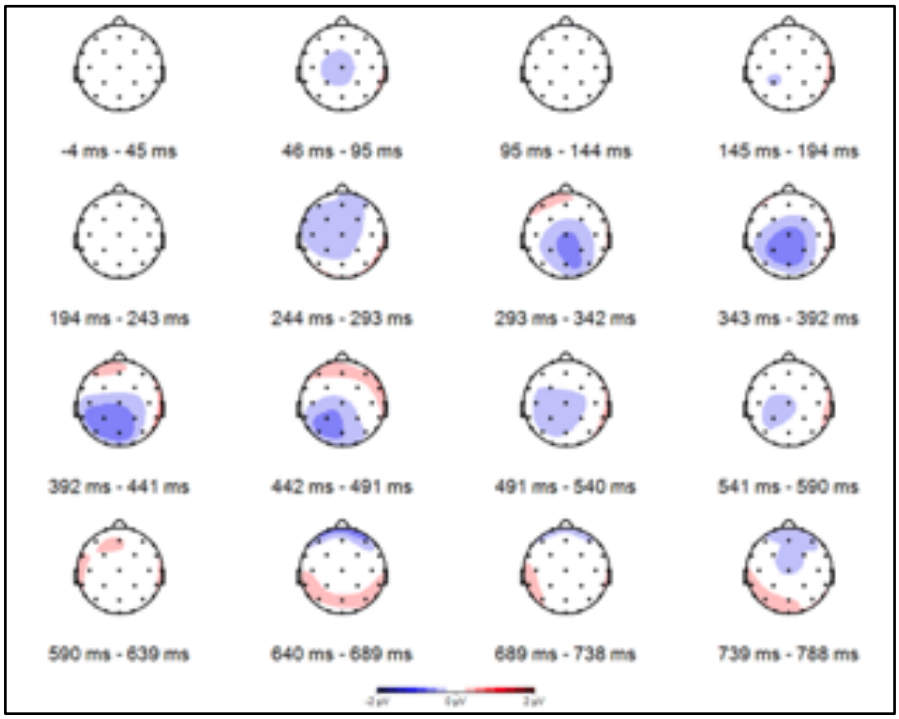
Descriptive data are presented in Table 1 and included number of participants, their age and education, as well as behavioural scores on the Raven test. ERP data are visually represented in Pictures 1 - 3. Statistical data are represented visually in Graphs 1 and 2. Numerical data were exported from the Brain Products Analyser 2 software in 150-200 ms and 250-350 ms time intervals for the purposes of statistical analysis. Statistical analysis consisted of GLM with placebo (placebo - no placebo) and congruency (congruent - incongruent) as two-level factors. Conditions in the measurement of the placebo effect were stimuli in the Stroop task: congruent, incongruent, and neutral. Neutral condition was not considered in this study. We attempted to establish whether there was a difference in attention measured by reaction time between congruent and incongruent conditions in placebo and no placebo conditions. Picture 1 shows the main effect of placebo response on the Fz, F4, Cz, and T8 electrodes. The placebo effect was obtained on all electrodes as shown on the distribution maps in Picture 2. Picture 1 contains only the electrodes where the placebo effect was shown to be statistically significant. The placebo effect is indicated by a modulation of the P2 and N2 components on the frontal electrodes in the 150-200 ms time interval. The difference between all four conditions was obtained in the latencies around 400 ms on the central electrodes.



Picture 1: ERP waveforms obtained in all four conditions (congruent – incongruent x placebo – no placebo: black: no placebo-congruent, red: no placebo-incongruent, blue: placebo-congruent, green: placebo-incongruent condition)



Picture 2: Distribution maps showing the placebo effect (congruent placebo minus congruent no placebo conditions)

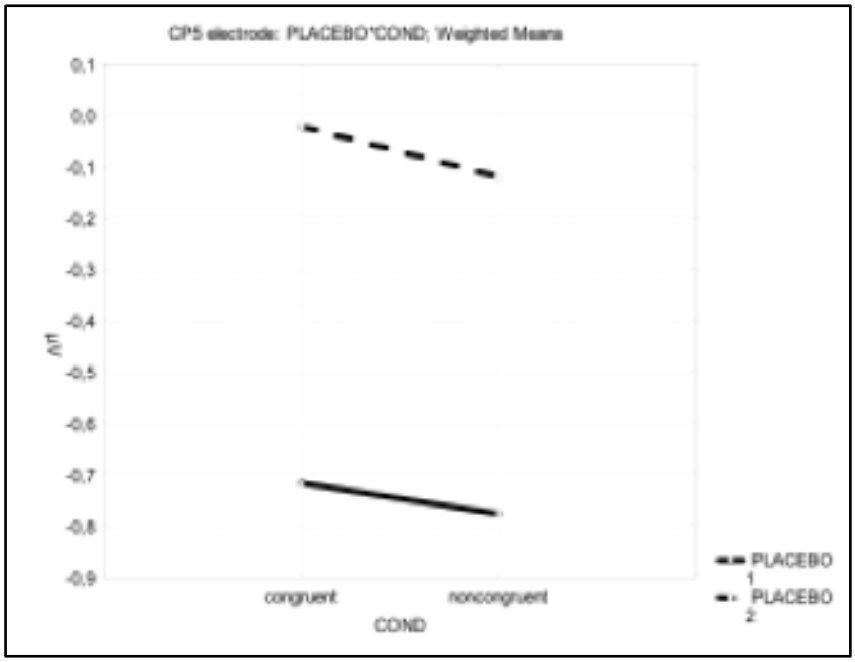


Picture 3: Congruency effect (difference map between congruent and incongruent conditions for no placebo conditions)

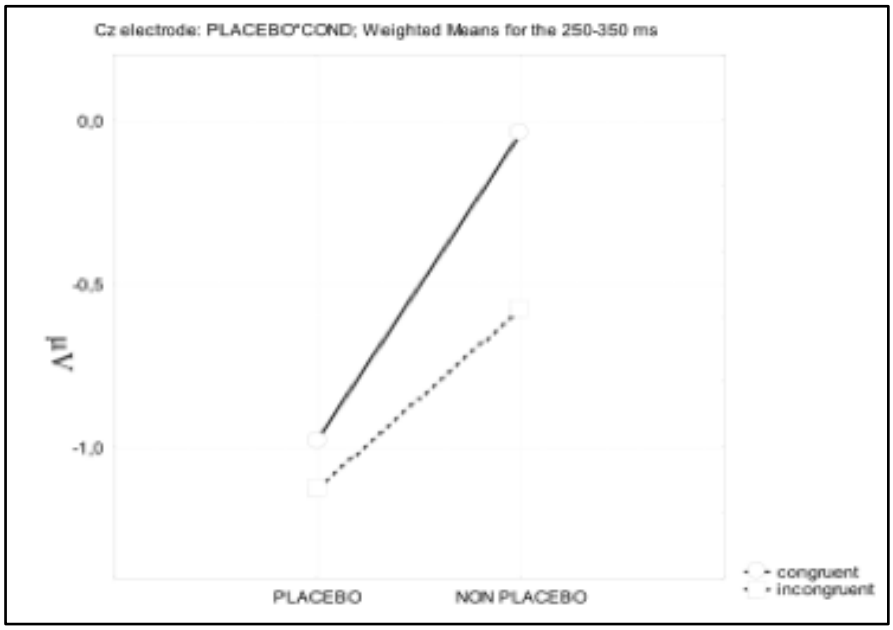
Picture 3 shows the congruency effect as a centro-parietal negativity in the 350-450 ms time interval. Note that the congruency effects are visibly weaker than the placebo effects. In addition, there are no effects on the early components (P2, N2). Pictures 2 and 3 represent topographically that the placebo effect is more significant in the frontal electrodes in earlier time intervals whereas more activity is evidenced in central electrodes in the later time intervals. Meanwhile, the congruency effect shows up in the later time interval in the frontal areas of the cortex.

6. Statistical analysis

Since the same groups of participants were involved in the placebo and no placebo conditions (two experiments on the same sample) we were able to use repeated measures ANOVA for the purpose of statistical analysis. The main effect of placebo was obtained on a number of electrodes (Fz, F4, Cz, T8, CP5) in the early time interval (150-200 ms). No interaction between the main effects was shown as significant. In the 350-450 ms window, the placebo main effect was significant on the P3 and P8 electrodes (P3: $F(1, 18) = 4.498$, $p = 0.048$; P8: $F(1, 18) = 7.055$, $p = 0.016$). Graph 1 shows the placebo effect, as obtained on the CP 5 electrode in congruent and incongruent conditions. Graph 2 shows the congruency effect, as obtained on the Cz electrode in the late time interval (250-350 ms).



Graph 1: Graphical representation of the main effect of placebo on CP5 ($F(1, 18)= 6.136$, $p = 0.023$)



Graph 2: Graphical representation of the main effect of congruency on Cz electrode in the 250-350 ms interval

7. Discussion

This study tried to capture the placebo effect on attention by measuring participants' reaction time during a Stroop task. The conditions of the Stroop task were image-word congruent, incongruent or neutral. We chose the evoked related potentials (ERP) technique in order to objectively establish the presence of the placebo effect on attentional processes by measuring cortical activity during placebo condition.

In general the focus of studying placebo lies in the field of clinical and medical problems, such as for pharmaceutical purposes and medical treatments. Because investigations of the placebo effect on cognitive functions in non-clinical populations are relatively few and the field has only recently been gaining more interest, the exact nature of the relationship between placebo effects and cognitive functions is still unclear. One example of this work is a study utilizing positron emission tomography, which found hemispheric differences during the response choice and found functional connections of left mid-cingular region with left insula and temporal and frontal cortex during cognitive interference (George et al., 2004). We attempted to extend this line of inquiry through the use of EEG/ERP technique. By using the Stroop task which is a well-established protocol for assessing attentional processes, our results are able to show the effect of placebo on attention. In other words, the present study found that attention can be modulated by placebo most likely related to participant expectations. The participants expected that taking the "Brain Improving Pill" would improve attention thereby improving reaction time on the Stroop task. These results allow us to speculate that the placebo effect facilitated the engagement of a larger neural network to solve the cognitive task at hand more efficiently. This is evidenced by higher amplitudes of N1, P2 and N400. In addition, the frontal distribution of the ERP effects speaks in favour of cognitive control being under the influence of placebo. The component P2 was obtained in other ERP studies of placebo, but related to pain stimuli (Lorenz & Garcia-Larrea, 2003; Wager et al., 2006; Wager et al., 2013). In these studies, the P2 component was interpreted in terms of cognitive control and expectations. Following the same line of reasoning about P2, we can assume that our "Brain Improving Pill" changed the expectations of our participants regarding their cognitive functioning. The role of expectations has been shown as very important in studying placebo in various settings, such as clinical and neuropharmacology (De Pascalis & Penna, 1990; Volkow et al., 2004).

We obtained significant placebo effects in frontal and parietal electrodes allowing us to conclude that frontal and parietal areas of the cortex were the most involved in the expectation processes related to placebo. We expected

that the electrodes connected to attention (frontal-temporal and parietal) would be associated with the experimental condition. The use of the ERP technique in the present study allowed for direct insights into cognitive functioning as modulated by placebo. In this sense, the present study is an extension of findings on the influence of placebo not only in pain research and other physiological applications, but also the impact of placebo on higher cognitive abilities.

The advantage of our study lies in the within-group design that is generally better for applying the ERP technique. In other words, the differences obtained between the placebo group and the control group could not have arisen from some subtle differences between groups. Future research should attempt to clarify what is the significance of the placebo effect on P3 and P8, given that the results of the present study and current theoretical and empirical level of understanding of placebo in cognitive functions are unable to shed light on this issue. The disadvantage of the study lies in the relatively small number of participants and the fact that they were all university students with average to high-average IQ and presumably strongly focused on academic success. In addition, a limitation of the study may be in the construction of the Stroop task itself. Given the congruency effects, it is possible that the task was too easy for the participants. For future studies it may be important to include potential mediators or predictors of the expectancy effect, i.e. stress level, anxiety level etc.

In conclusion, our study established the presence of the placebo effect in attentional processes and showed that future studies could focus on more precisely defining the neural correlates of placebo.

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