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ERP CORRELATES OF PLACEBO AND "ANTI–PLACEBO" EFFECTS[3]

In the study we observed the effects of placebo and "anti-placebo" messages on the neural activities registered through the event related potentials (ERP). Instead of commonly used term nocebo, we used the term "anti-placebo", given that the message we delivered was not supposed to induce the negative effects, but just to diminish the effect of placebo.

Thermal stimulus of 45 degrees of Celsius was applied on the skin of 29 students in a four different experimental situations: without analgesia, after receiving dermal analgesic EMLA Cream, after receiving neutral skin cream presented as an analgesic (placebo situation), and after receiving again EMLA Cream, but presented as the herbal analgesic not officially accepted as a medicament ("anti-placebo" situation). Immediately after stimulation, participants were asked to estimate the level of "unpleasantness" of the stimuli on the subjective scale ranging from 1-10, and to start a cognitive experiment, during which the ERP responses were measured.

Results showed three main ERP effects. In the early effect, we noticed that all three experimental situations with analgesia (that is, two conditions with the pharmaco-analgesia + the condition with the placebo analgesia) showed a different ERP effects in comparison to the condition with no analgesia. We interpreted these results as early expectancies that any analgesic (including placebo) should produce some effect in comparison to no-analgesic condition. In the medium effect, we observed significantly longer durations of the ERP effects in the situation of the "anti-placebo" and no-analgesia, whereas in the analgesia and placebo condition these effects were much shorter. This result led us to the conclusion, that

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on the neural level, our suggestion of "bad medicament" (similar to situation of no-medicament) caused a specific mental activity registered on ERP. This effect is the one which calls into a question doctors' recommendations (which contain negative connotation) of medicaments, as they could potentially and unconsciously diminish a valuable impact that the placebo could have during a treatment. Finally, in the late effect, we also observed significant differences across the four experimental conditions, but these differences were directly correspondent with the order of presentation of experimental situations, and we interpret them as an artefact of the experimental design.

Keywords: placebo, analgesics, thermal stimulus, ERP

Despite the fact that placebo (Latin for "I shall please.") was known in medicine for hundreds of years now, and pharmacology implicitly assumed its impact on the effect of medication (which was controlled in evaluation of the medicament), the true scientific interest in the nature and mechanisms of placebo effects started only after Henry Beecher (1955), published his influential paper "The powerful placebo". He demonstrated that patients of doctors he categorized as "enthusiasts" relieved their patients' chest pain and heart problems more than skeptic doctors. In the light of this finding, placebo could be considered as a useful instrumentality through which the impact of medicaments (and doctors) could be intensified and that way be of great benefit to the patients. In his editorial BMJ devoted to placebo effects, Spiegel (2004) wrote: "We cannot afford to dispense with any treatment that works, even if we are not certain how it does."

Basically, in the core of the placebo effect is the patient's expectancy that the medicament will have an effect. These expectancies could be absurd, like for example, misbelief that the ultrasound could have anti-inflammatory effects and when that misbelief truly results in such an effect (Hashish, Harvey, & Harris, 1986)! But, as we mentioned already, effect of (positive) expectancies could be of great use in therapy, because it is proven that analgesics have much stronger effects when patients are aware that they are consuming them that when they are uninformed of the medicament treatment (Colloca, Lopiano, Lanotte, & Benedetti, 2004).

However, expectancy is psychological, not medical term (similar to suggestion which was also related to expectancy) and its mechanism is not all that clear. That is why the placebo was often explained through a conditional reflex in those patients who had a positive effect of medicament (Voudouris, Peck, & Coleman, 1989) or, in a worst case scenario, it's effect was completely denied (Hróbjartsson & Gøtzsche, 2001). Nonetheless, since Levine, Gordon, and Fields (1978) demonstrated that the opioid antagonist naloxone could block placebo painkillers, suggesting that endogenous opioids are involved, there is no doubt that placebo effect has neurobiological base.

After that, we have witnessed a series of studies that used up-to-date neuroimaging and neurophysiological methodologies such as functional neuro-magnetic resonance (fMRI), positron emission tomography (PET), and evoked related potentials (ERP) (see reviews: Beauregard, 2007; Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005; Enck, Benedetti, & Schedlowski, 2008; Price, Finiss, & Benedetti, 2008).

The first studies with PET methodology (Petrovic, Kalso, Petersson, & Ingvar, 2002), already demonstrated that there are 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. One of the best demonstrations of placebo induced release of endogenous opioids, by using in vivo receptor binding with PET, was presented in the research reported by Zubieta et al. (2005). Increases of μ-opioid receptor neurotransmission were

found in anterior cingulate cortex, orbitofrontal cortex, the insula, and the nucleus accumbens.

On the other hand, fMRI studies (e.g. Wager et al., 2004) showed placebo effects as a result of activities in the orbitofrontal and dorsolateral prefrontal cortex during the anticipatory phase which precedes reductions in the activity of pain-responsive regions (the rostral anterior cingulate cortex, the insular cortex, and the thalamus) while subjects underwent a painful heat stimulus.

There have been many fewer studies using ERP methodology, possibly because they are less illustrative in pinpointing neurobiological mechanisms of the pain, analgesia and placebo. Wager, Matre, and Casey (2006), for example, demonstrated that, in comparison with the group with no analgesia, placebo treatment produced a significant decreases in P2 amplitude, and that P2 placebo responses were large enough to reflect a meaningful difference in nociceptive processing. According to Wager et al. (2006), one of the main characteristics of placebo effects is that they can induce an affective/motivational state which leads to reduced attention to pain. They further claim that such motivational state, which regulates the allocation of attention, seems to be only partially under voluntary control ("e.g., it is very difficult to wilfully ignore a rattlesnake next to one's foot."). And, in such a scenario, the placebo effects play a role of safety signals which permit attention to be directed away from pain. Finally, Wager et al. (2006) concluded that placebo effects registered in the mid-frontal P2 region would be consistent with this view. The role of the behavioural context (i.e., factors that affect motivated attention), which inspired Wager et al.'s (2006) work was described by Duncan, Bushnell, Bates, and Dubner (1987) who showed that behavioural context affects sensory pathways in the dorsal spinal horn. According to those studies, attentional frame can have far-reaching physiological effects. Moreover, as a result of numerous studies, we have witnessed a development of another, parallel concept – nocebo effect (Latin for "I will harm.") which implies development of adverse events or worsening of a condition after the administration of a placebo. It appeared with the demonstration that the placebo "imitation" can not only produce the medicament effects, but its side-(harmful) effects as well! The neuroimaging studies which clearly demonstrated the existence of nocebo effects followed. For example, Sawamoto et al. (2000) demonstrated that expectation of a painful stimulus amplified the perceived unpleasantness of innocuous thermal stimulation, and that these subjective hyperalgesic reports were accompanied by increased brain activations in the anterior cingulate cortex, the parietal operculum, and posterior insula. In one of the recent studies, Scott, Stohler, Egnatuk, Wang, Koeppe, and Zubieta (2008) concluded that the high placebo responses were associated with greater dopaminergic and opioid activity in the nucleus accumbens, while nocebo responses were associated with a deactivation of dopaminergic systems and opioid release. Pharmacological studies (e.g. Benedetti, Lanotte, Lopiano, & Colloca, 2007) showed that suggestions of a positive outcome (pain decrease) activate endogenous μ-opioid neurotransmission, while suggestions of a negative outcome (pain increase) activate CCK-A and/or CCK-B receptors.

Based on the above described sensitivity of placebo effects on the behavioural context which can lead to reduced attention to pain and which was registered through P300 ERP component, in the present study we observed the effects of placebo and "anti-placebo" messages on the neural activities registered through the event related potentials (ERP). We used the visual odd-ball paradigm task which is well known to modulate the P300 effect. Thus, the main idea was to register if the "anti-placebo" messages would evoke different neural correlates (registered through the amplitude and latency of P300 effect) in comparison to placebo effects and baseline conditions (in which analgesia or no analgesia was applied). Instead of commonly used term nocebo, we decided to use the term "anti-placebo", given that the message we delivered was not supposed to induce the negative effects, but just to diminish the effect of placebo.

Method

Participants

We recruited 29 students from the Department of Psychology, University of Novi Sad, Serbia, who received course credits for their participation and who signed the informed consent prior to their participation in the study. These students were selected from a bigger sample and the selection criterion was that they were similarly sensitive (4–7 on a subjective scale from 1–10) to the thermal stimulation of 45 degrees of Celsius (which they were exposed to in the experiment).

Instruments

The instrument for delivery of the thermal stimulus. For the application of the thermal stimulation we used an instrument specially created for this study at the Faculty of Technical Sciences, University of Novi Sad. It consists of an electrode (0.5 cm x 0.5 cm) at the end of a 4 m long isolated wire, connected with a small generator which enables manual adjustment of the intensity of heat, which is digitally recorded and observable on the small display of the instrument.

Electrophysiological recording. For the purposes of measurement of ERPs, we used NeuroIM-1 system also developed at the Faculty of Technical Sciences, University of Novi Sad. NeuroIM-1 system for measurement and processing is intended for extracting ERP on the base of recordings from electrodes positioned on international 10–20 system locations. In its current version, it is designed as one channel system, and its main properties are 0.015–70 Hz bandwidth of the amplifier, and 256 Hz sampling frequency (for the detailed description of the ERP system see Sovilj, Davidović, Beljić, & Ković, 2011).

Procedure

Prior to the experiment, participants were informed that the study was aimed at testing neural activities during various analgesic applications, and that they will take part in odd-ball paradigm task which was known to be sensitive to participant`s expectancies of the frequency of the stimuli appearance.

Participants were seated in a darkness of a specially designed sound-isolated Faraday cage cubical, approximately 80 cm away from an experimental monitor. There were four experimental conditions in which thermal stimulation of 45 degrees of Celsius was applied on the skin of the participant's forearm for the duration of 1 second. In the first experimental condition, participants were not given any analgesic; in the second, they received well-known dermal analgesic – EMLA Cream, Sweden made; in the third situation, they received a neutral skin cream presented as "a new analgesic – Dermanalgetic (made-up name), Swiss made"; and in the fourth experimental condition they received again EMLA Cream, but presented as "the herbal-based analgesic Tangva (also made-up name), Vietnam made, production which is not registered as medicament and cannot be purchased in regular pharmacies". All three creams were applied one hour before the start of the experiment on the 1 cm^2 skin surface, 3 cm apart from one another. The third of the listed experimental situation was placebo situation, and the fourth experimental situation was "anti-placebo" situation.

Subjective assessment of "unpleasantness" was measured on the scale from 1–10 right after exposure to thermal stimulation. Participants were instructed to start the cognitive experiment immediately after their estimation of "unpleasantness".

Visual stimuli were presented through a small window of the cubical on the monitor which was placed outside of the cubical. The EEG data were recorded continuously from the CZ electrode and subsequently analysed.

After the completion of the experiment, participants were asked to give their impressions about the purpose of the experiment, so that we could check if the experimental manipulation was successful. From their responses, we concluded that none of the participants was aware of the main manipulation.

Design of the cognitive experiment. Participants were presented with the sequences of stimuli consisting of 80 per cent of standard (i.e. frequent stimuli, in this case Xs) and 20 per cent of deviant (i.e. infrequent stimuli, in this case Os), and they were supposed to respond only when presented with the deviant stimuli. The time sequence of presentation was as following: a fixation cross was presented to participants for a variable amount of time: 500±100 ms. This variation (i.e. jittering) was introduced to prevent preparatory motor responses given that participants can easily get into the rhythm of the task and be ready to respond before the stimulus presentation which is then strongly reflected through the participants' brain waves, masking the task effects (Luck, 2005). Just after presentation of the fixation cross, participants were presented with

the visual stimulus for the duration of 400 ms. After the stimulus presentation, a blank screen was presented for a variable amount of time (500±100 ms).

Results

All the recorded stimuli were subsequently cut into the epochs (100 for each participant, for each experimental procedure) and all the epochs containing the noise such as participants' motor movements, eye-blinks, drifts etc. were manually eliminated from the analysis. The percentage of the elimination of the noise for all the participants who took part in this study was less than 5%. The epochs were base-lined at the 200 ms prior to the stimulus presentation.

In the very first step of the analysis all of the epochs were cut into 24 ms windows intervals, so that the total number of the analysed intervals were 40 (8 prior to presentation of the stimuli and 32 after the stimulus presentation, see Kovic, Plunkett, & Westermann (2010) for the more detailed description of the interval-by-interval analysis). Given the multiple comparisons, Bonferroni corrections were also applied. Finally, we reported significant differences only if the neighbouring 20 ms bins were significant at the $p < .05$ level (Eddy, Schmid, & Holcomb, 2006).

The analysis revealed significant differences within three intervals, which we refer to as early, medium and late effect (Figure 1).

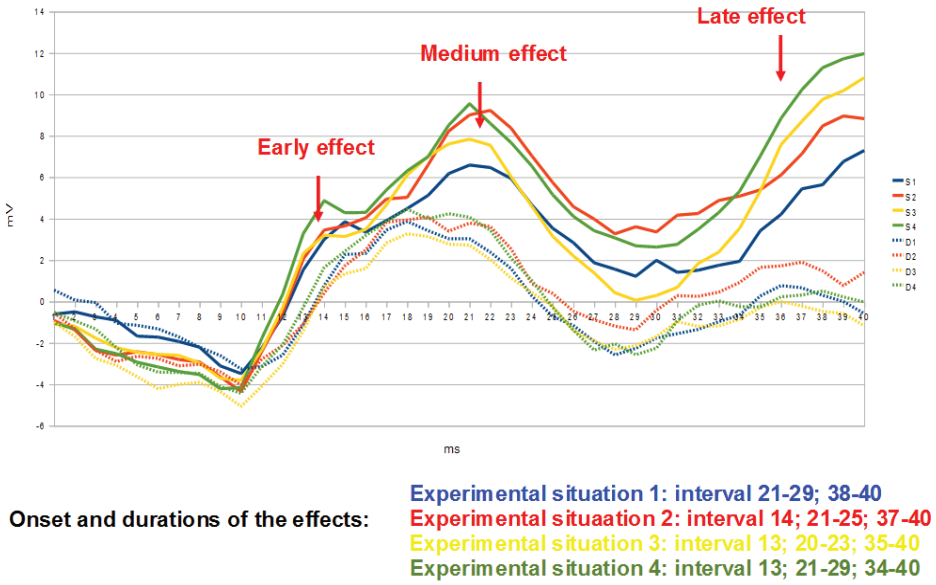


Figure 1. ERP profiles for standards and deviants for the four experimental procedures: early, medium and late effects

Regarding the early effect, the significant amplitude differences (in microvoltes) between standard and deviant stimuli were observed within the interval 13 (for the third experimental condition – placebo: $t(1, 54) = 3.94$, $p < .001$; and for the fourth experimental condition – "anti-placebo": $t(1, 56) = 3.18$, $p < .01$) as well as within the interval 14 for the second experimental condition – analgesic: $t(1, 56) = 3.64$, $p < .01$, see Figures 2a and 2b. The only condition in which no differences were observed during these early intervals was the first experimental condition in which no analgesia was applied ($p > .05$).

Similarly, on the scale (1–10) of the subjective judgment of the level of "unpleasantness", after application of the thermal stimuli of 45 degrees of Celsius, the first experimental condition differed from the other three ($p < .05$). The mean judgment for the first experimental groups was: 4.44 and for the analgesia, placebo and "anti-placebo" groups judgments were: 2.86, 2.96 and 2.86, respectively.

The medium ERP effect revealed different onsets and latencies of the ERP amplitudes across the four experimental conditions between standard and deviant stimuli. For the first, no-analgesia condition, the effect started from the 21st interval and lasted till the 29th interval. For the second, analgesia condition, the effect also started from the 21st interval, but lasted shorter, till the 25th interval. In the third, placebo condition the effects started earlier, from the 20th interval and lasted shorter, till the 23rd interval. Finally, in the fourth, "anti-placebo" condition, the effect started from the 21st and lasted till the 29th interval, just as in the first experimental condition. All these differences were significant at the $p < .05$ level.

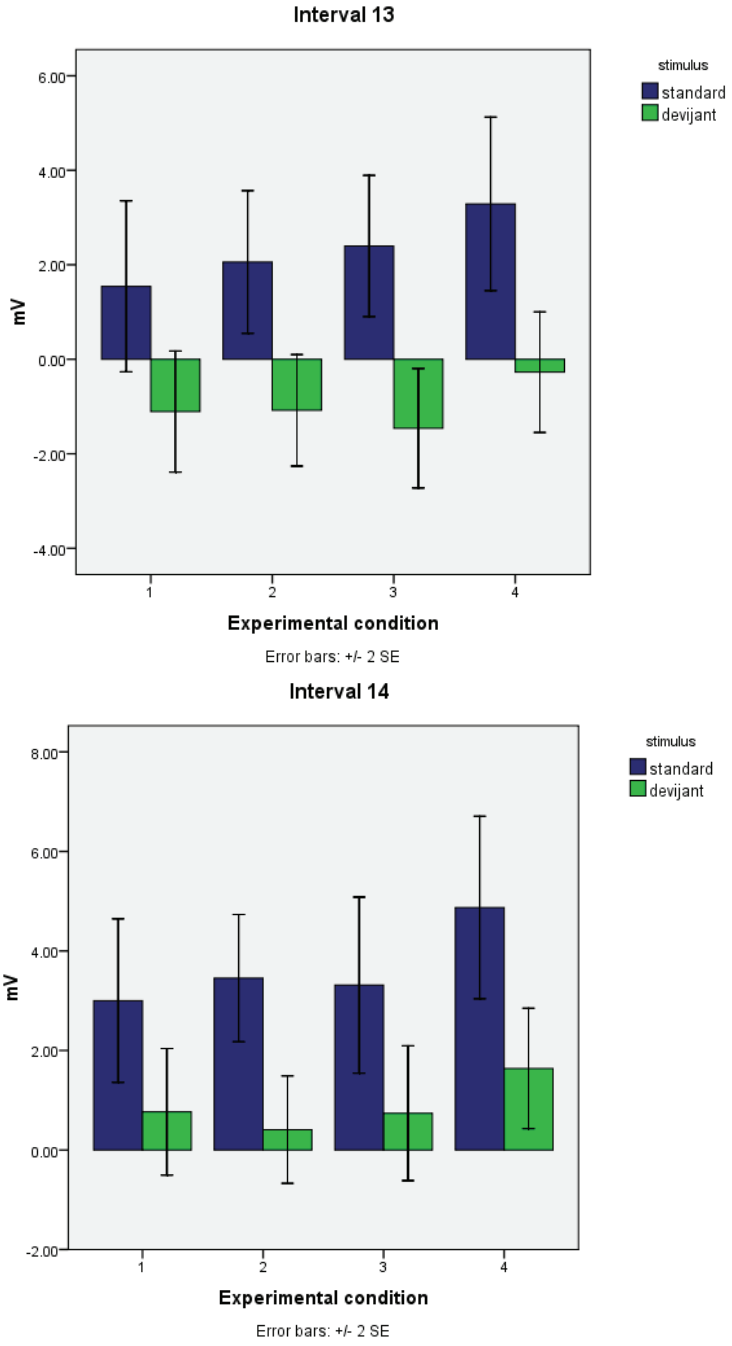
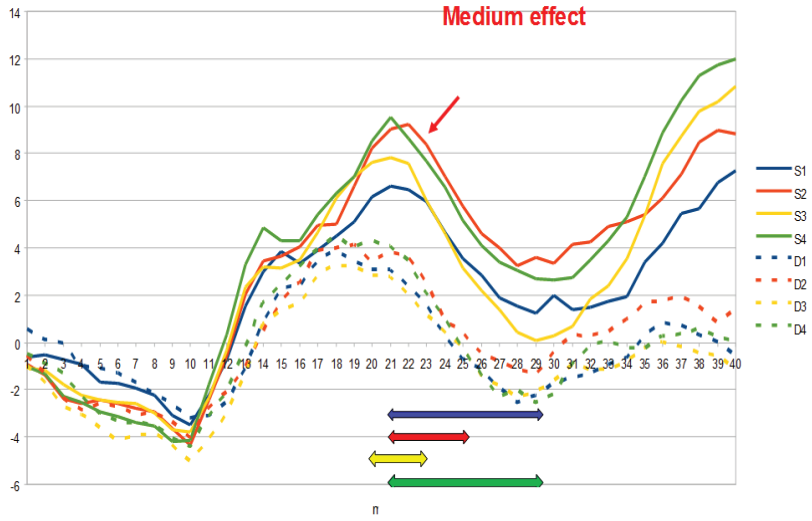


Figure 2a and 2b. ERP profiles for standards and deviants for the four experimental procedures for the intervals 13 and 14 respectively



Onset and duration of the effects:

Experimental procedure 1: interval 21-29; 38-40
Experimental procedure 2: interval 14; 21-25; 37-40
Experimental procedure 3: interval 13; 20-23; 35-40
Experimental procedure: interval 13; 21-29; 34-40

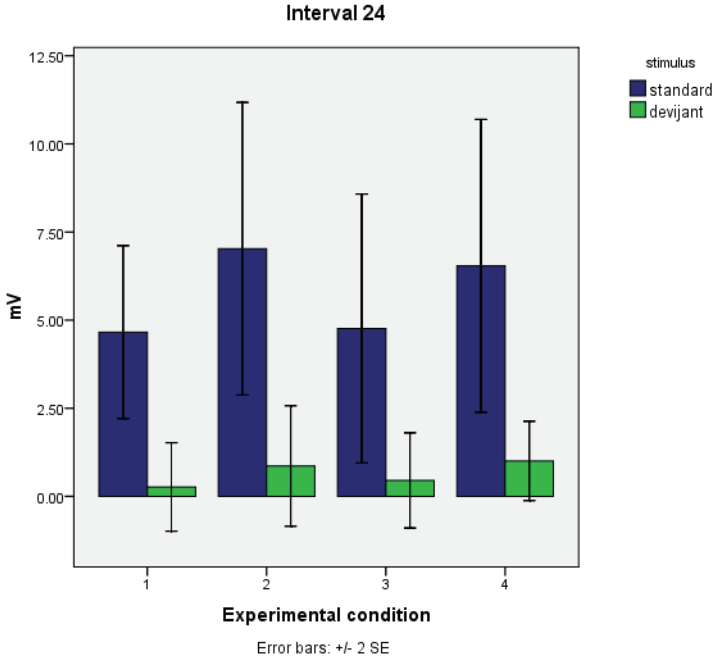


Figure 3a and 3b. ERP profiles for medium effects for standards and deviants for the four experimental procedures and exemplary statistics for the interval 24

The illustration of the onsets and latencies of the medium effects is shown in the Figure 3a as well as the statistics for the interval 24 in the Figure 3b. Thus, for the interval 24 we observed differences between standards and deviants in the first ($t(1, 56) = 3.19$, $p < .01$), second ($t(1, 56) = 2.75$, $p < .01$) and in the fourth experimental condition ($t(1, 56) = 2.57$, $p < .05$).

Finally, we also observed the late effects of the ERP amplitudes across the four experimental conditions. For the first, no-analgesia condition, the late effect started from the 38th interval and lasted till the 40th interval. For the second, analgesia condition, the effect started from the 37th interval and lasted till the 40th interval. In the third, placebo condition the effects started earlier, from the 35th interval and lasted till the 40th interval. Finally, in the fourth, "anti-placebo" condition, the effect also started earlier from the 34th interval and lasted till the 40th interval. Again, all these differences were significant at the $p < .05$ level. For the illustration, in the Figure 4 we gave statistics for the differences between standards and deviants for the 40th interval across the four experimental conditions (no-analgesia: $t(1, 56) = 4.20$, $p < .001$; analgesia: $t(1, 56) = 2.85$, $p < .01$; placebo: $t(1, 54) = 3.613$, $p < .01$; "anti-placebo": $t(1, 56) = 3.46$, $p < .001$).

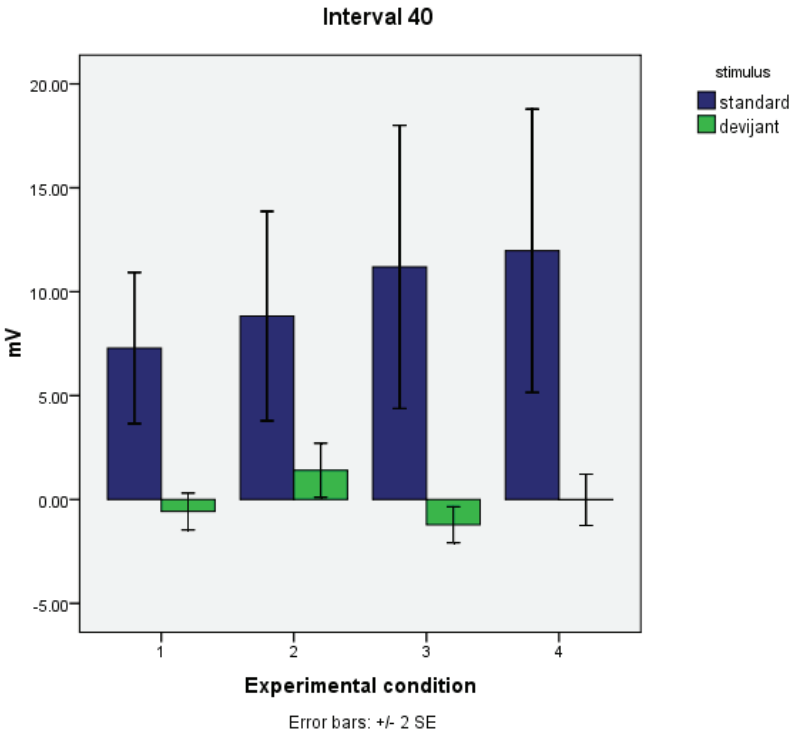


Figure 4. The mean amplitudes for the standards and deviants across the four experimental conditions for the interval 40

Similarly, when we compared the reaction times across the four experimental conditions we found the significant main effect of experimental condition ($F(3, 111) = 2.97$; $p < .05$), with significant differences between first and forth ($p < .01$) and first and third experimental condition ($p < .05$), meaning that the final experimental procedure, "anti-placebo", led to the quickest RT responses, significantly differing from the no-analgesia and analgesia procedures (see Figure 5).

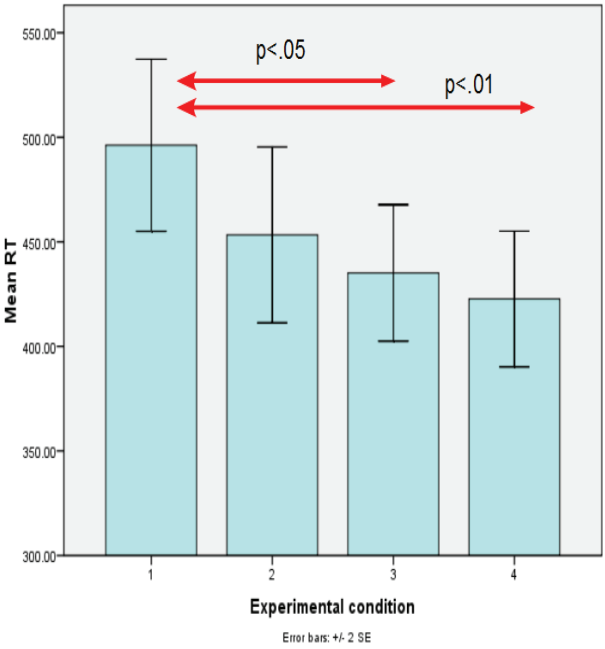


Figure 5. RTs across the four experimental conditions

Discussion and Conclusions

The ERP studies investigating neural correlates of placebo effects are very rare. Moreover, those rare studies are mainly focusing on the ERP responses which are locked to the distribution of the pain (e.g. Brown, Seymour, Boyle, El-Deredy, & Jones, 2008; Wager et al., 2006). However, in this study we were predominantly interested in the psychological aspect of the placebo and "anti-placebo" and we investigated those effects simply by modulating the message that we gave to the participants. The second important novelty of this study is that we were not only interested in the effects that placebo messages have on the neural activities registered through the event related potentials. We were predominately interested in learning if "anti-placebo" messages could modulate or diminish placebo effects unconsciously (i.e. on the neural level), through the instruction

that was delivered by an experimenter in strictly controlled conditions. If so, that could and should have very serious consequences as to which kind of messages and recommendations are doctors are allowed to give to their patients. Consequently, this stream of research could lead to important recommendations to the medical ethical guidelines, but also to a broader public as well. Thus, the main motivation behind this study was to test if doctor's recommendation that the medicament is "not as good as some other", could diminish the placebo effect which is known to be related to the basic pharmacological effect of medicament.

The first and foremost conclusion that we can draw from our pioneering study in this field is that we registered distinct neural correlates of analgesia/expectancy of analgesia based on the different profiles of the ERP waveforms. All three experimental situations with analgesia (that is, two conditions with the pharmaco-analgesia + the condition with the placebo analgesia) showed different ERP early effects in comparison to the condition with no analgesia. Moreover, this result is correspondent with the subjective judgement of the "unpleasantness" (for which we used 1–10 scale). Interestingly, neither in the early ERP effects, nor in the subjective judgement, does the placebo effect differ from the pharmaco-analgesia. Thus, although we did not have a specific hypothesis regarding such an early effect, we interpreted these results as early expectancies that any analgesic should produce some effect in comparison to no-analgesic condition.

On the other hand, in the subjective judgement we did not register effects of "anti-placebo". However, in the medium ERP effects we observed prominently distinct "anti-placebo" and no-analgesia effects in comparison to the analgesia and placebo effects. Namely, we observed significantly longer durations of the medium ERP effects in the situation of the "anti-placebo" and no-analgesia (in both conditions the ERP effects lasted from 21–29 interval – thus, over 200 ms), whereas in the analgesia and placebo condition these effects were much shorter – (half shorter in the analgesia condition (21–25 interval) and even shorter in the placebo condition (20–23 interval), respectively. Obviously, according to the subjective judgement of the unpleasantness, we did not manage to convince our participants that the medicament they hade received was "of the lower-quality". However, neural correlates, or their unconsciousness responses revealed that the duration of the effects in the absence of analgesia and in the "anti-placebo" situation are identical. This result led us to the conclusion, that on the neural level, our suggestion of "bad medicament" (similar to situation of no-medicament) caused a mental activity which, figuratively, we could interpret as a worry-response – "Is this still going to hurt me?". This effect led us to a following speculation: If experimenter's manipulation triggers such neural effects, doctors' recommendations (which contain negative connotation) of medicaments, could also potentially and unconsciously diminish a valuable impact that the placebo could have during a treatment.

In the late ERP effect, we also observed significant differences across the four experimental conditions and these differences were directly correspondent to the order of presentation of experimental situations. The same effect is present in the

RT analysis, whereby participants became progressively faster as they advanced through the experiment. Here we conclude that both in the RTs and in the late ERP effects we see the effects of training which speed up participants' performance and lead to the expectancy of the end of the presented epochs. This hypothesis is worthwhile testing in future studies in which the order of the experimental situations should be counterbalanced across the participants. In the present study, we were particularly cautious that participants do not become aware of the main manipulation and hence the order of the presentation was fixed – starting with no analgesia, followed by analgesia, placebo, and finally "anti-placebo" effects. Lastly,, this study calls into question the neural correlates of the "anti-placebo" effects which would be directly related to the pain, rather than to a psychological effect of the message to the participants, which was the main focus of the present studies. As mentioned earlier, to our best knowledge, this is the first ERP study attempting to observe neural correlates of the "anti-placebo" effects.

References

Beauregard, M. (2007). Mind does really matter: Evidence from neuroimaging studies of emotional self-regulation, psychotherapy and placebo effect. *Progress in Neurobiology, 81*, 218–236.

Beecher, H. K. (1955). The powerful placebo. *JAMA, 159*, 1602–1606.

Benedetti, F., Lanotte, M., Lopiano, L., & Colloca, L. (2007). When words are painful – unraveling the mechanisms of the nocebo effect. *Neuroscience, 147*, 260–271.

Benedetti, F., Mayberg, H. S., Wager, T. D., Stohler, C. S., & Zubieta, J. K. (2005). Neurobiological mechanisms of the placebo effect. *Journal of Neuroscience, 25*, 10390–10402.

Brown, C. A., Seymour, B., Boyle, Y., El-Deredy, W., & Jones, A. K. (2008). Modulation of pain ratings by expectation and uncertainty: Behavioral characteristics and anticipatory neural correlates. *Pain, 135*, 240–250.

Colloca, L., Lopiano, L., Lanotte, M., & Benedetti, F. (2004). Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurology, 3*, 679–684.

Duncan, G. H., Bushnell, M. C., Bates, R., & Dubner, R. (1987). Task-related responses of monkey medullary dorsal horn neurons. *Journal of Neurophysiology*, *57*, 289–310.

Eddy, M., Schmid, A., & Holcomb, P. J. (2006). Masked repetition priming and event-related brain potentials: A new approach for tracking the time-course of object perception. *Psychophysiology, 43,* 564–568.

Enck, P., Benedetti, F., & Schedlowski, M. (2008). New insights into the placebo and nocebo responses. *Neuron, 59*, 195–206.

Hashish, I., Harvey, W., & Harris, M. (1986). Anti-inflammatory effects of ultrasound therapy: evidence for a major placebo effect. *British Journal of Rheumatology, 25*, 77–81.

Hróbjartsson, A., & Gøtzsche, P. C. (2001). Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *New England Journal of Medicine, 344*, 1594–1602.

Kovic, V., Plunkett, K., & Westermann, G. (2010). The shape of words in the brain. *Cognition, 114*, 19–28.

Levine, J. D., Gordon, N. C., & Fields, H. L. (1978). The mechanisms of placebo analgesia. *Lancet, 2*, 654–657.

Luck, S. J. (2005). *An introduction to event-related potentials and their neural origins.* Boston: MIT Press.

Petrovic, P., Kalso, E., Petersson, K. M., & Ingvar, M. (2002). Placebo and opioid analgesia – imaging a shared neuronal network. *Science, 295*, 1737–1740.

Price, D. D., Finiss, D. G., & Benedetti, F. (2008). A comprehensive review of the placebo effect: Recent advances and current thought. *Annual Review of Psychology, 59*, 565–590.

Sawamoto, N., Honda, M., Okada, T., Hanakawa, T., Kanda, M., Fukuyama, H., . . . Shibasaki, H. (2000). Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulated cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. *Journal of Neuroscience, 20*, 7438–7445.

Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., & Zubieta, J. K. (2008). Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Archives of General Psychiatry, 65*, 220–231.

Sovilj, P., Davidović, D., Beljić, Ž., & Ković, V. (2011). Measurement and processing of event-related brain potential records. *Proceedings of the Telfor 2011*, 683–686.

Spiegel, D. (2004). Placebos in practice. *British Medical Journal, 329*, 927–928.

Voudouris, N. J., Peck, C. L., & Coleman, G. (1989). Conditioned response models of placebo phenomena: further support. *Pain, 38*, 109–116.

Wager, T. D., Matre, D., & Casey, K. L. (2006). Placebo effects in laser-evoked pain potentials. *Brain, Behavior, and Immunity, 20*, 219–230.

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., . . . Cohen, J. D. (2004). Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science, 303*, 1162–1167.

Zubieta, J. K., Bueller, J. A., Jackson, L. R., Scott, D. J., Xu, Y., Koeppe, R. A., & Stohler, C. S. (2005). Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. *Journal of Neuroscience, 25*, 7754–7762.

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ERP KORELATI PLACEBO I „ANTI–PLACEBO" EFEKATA

U ovom istraživanju bavili smo se neuralnim korelatima efekata placebo i „anti-placebo" poruka putem merenja moždanih talasa (ERP). Umjesto uobičajenog termina nocebo, koristili smo termin „anti-placebo", budući da poruke koje smo zadavali ispitanicima nisu trebale da proizvedu negativne efekte, već da umanje ili poništе efekat placeba. Primenili smo termalnu draž intenziteta 45 stepeni Celzijusa na kožu podlaktice. Ukupno je 29 studenata uzelo učešća u četiri eksperimentalne situacije: bez analgezije, nakon primene analgezije (korišćenjem EMLA kreme), nakon primene neutralne kreme koja je prezentovana kao analgetik (placebo situacija) i nakon primene EMLA kreme koja je prezentovana kao herbalna krema koja nije zvanično prihvaćena kao medikament („anti-placebo" situacija). Neposredno nakon stimulacije, od ispitanika je zatraženo da procene nivo neprijatnosti na subjektivnoj skali osetljivosti 1–10, a nakon toga im je zadat kognitivni eksperiment, tokom koga su mereni ERP odgovori.

Rezultati su pokazali tri glavna ERP efekta. U ranom efektu, sve tri eksperimentalne situacije koje su podrazumevale primenu anelgezije (tj. dve situacije sa farmako-anelgezijom + situacija sa placebo-aneglezijom) pokazale su različite profile ERP efekata u odnosu na situaciju u kojoj nije primenjena anelgezija. Ovaj rezultat smo interpretirali kao rano očekivanje da bilo koja vrsta anelgezije (uključujući placebo) treba da proizvede nekakav efekat, za razliku od situacije u kojoj nije bilo primene analgezije. Središnji ERP efekat je demonstrirao duže trajanje ERP efekata u situaciji sa „anti-placebom" i u situaciji bez analgezije, dok su u situaciji sa primenom analgezije i u placebo situaciji ovi efekti bili mnogo kraći. Ovaj nas je rezultat naveo na zaključak da, na neuralnom planu, sugerisanje da je neki lek „anti-placebo" proizvodi sličan profil ERP ili sličnu mentalnu aktivnost kao u situaciji bez leka. Ovaj rezultat poziva na preispitivanje preporuka lekara da neki lekovi nisu baš dobri, jer ovakve sugestije mogu potencijalno i nesvesno da umanje inače pozitivan efekat koji placebo ima tokom tretmana. Na kraju, u poznom efektu smo takođe uočili razlike između četiri eksperimentalne situacije, ali su ove razlike u vezi sa redosledom izlaganja eksperimentalnih situacija, te smo ih interpretirali kao artefakt eksperimentalnog dizajna.

Ključne reči: placebo, analgetici, toplotni stimulus, ERP