The Journal of General Psychology

ISSN: 0022-1309 (Print) 1940-0888 (Online) Journal homepage: https://www.tandfonline.com/loi/vgen20

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To cite this article: Attila Szabo, Lilla Jobbágy & Ferenc Köteles (2018) Super Pill is Less Effective than an Ordinary Mint in Altering Subjective Psychological Feeling States within a Few Minutes, The Journal of General Psychology, 145:2, 208-222, DOI: 10.1080/00221309.2018.1459454

To link to this article: https://doi.org/10.1080/00221309.2018.1459454

Published online: 16 May 2018.

THE JOURNAL OF GENERAL PSYCHOLOGY
2018, VOL. 145, NO. 2, 208–222
https://doi.org/10.1080/00221309.2018.1459454

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Super Pill is Less Effective than an Ordinary Mint in Altering Subjective Psychological Feeling States within a Few Minutes

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ABSTRACT

Expectations shape human behavior. Initial drug use might be associated with information-based expectations. In this study, we presumed that changes in affect and perceived physical wellbeing will be stronger after receiving an active placebo (*Tic Tac* mint; $n = 40$), than a pure placebo (inert pill; $n = 40$) given as a mood-enhancing "super pill." After baseline measures, participants completed a treatment-expectancy scale, ingested the mint/super pill, and attended to the effects over 3-minutes. Subsequently, they completed again the psychological tests. Expectancy scores were positive and did not differ between the groups. The pure placebo group increased in physical wellbeing but less than the active placebo group, which also showed an increase in positive affect. Negative affect decreased in both groups. The *Tic Tac* produced greater affective changes than the pure placebo. Since these are new findings on the ultra-short placebo effects on affect, the results might have relevance for drug-use studies.

ARTICLE HISTORY
Received 13 January 2018
Accepted 3 March 2018

KEYWORDS
Beliefs; drug effect; expectation; ingestion; pill

The Expectancy Theory was conceptualized in a social learning framework (Bandura, 1977). It is an amalgam of learning and subjective cognitive-neural processes (White, Bates, & Johnson, 1990). The theory explains human behavior via people's expectations of rewarding effects attributed to their actions. Whether the expectations are based on personal experiences, observation, persuasion, or rationally derived is unimportant (Humphrey, 2002). To influence behavior, they simply need to be held (Jones, Corbin, & Fromme, 2001). Neurophysiological evidence suggests that expectations increase brain glucose metabolism by 50%, especially in the thalamus region, which is involved in reward and conditioned responses (Volkow et al., 2003). The subjective certainty of an outcome (i.e., the strength of an expectation) appears to be key mediator of the results, since different brain regions are activated by certain and less certain expectations (Ploghaus, Becerra, Borras, & Borsook, 2003).

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Expectations that modify the neural processes in the brain are also involved in the placebo response (Atlas, & Wager, 2012; Benedetti, 2009; Stewart-Williams & Podd, 2004). Placebos are treatments, or interventions, that have no specific (i.e. pharmacological and/or biochemical) effect on the target condition (Ross & Olson, 1981). Instead, placebo reactions are evoked by the symbolic features, or the meanings, attached to the treatments (Brody & Brody, 2000; Moerman, 2002). Symbols are acquired by learning and can modify behavior through conscious and non-conscious processes (Stewart-Williams, 2004; Steward-Williams & Podd, 2004). Although other interpretations also exist (e.g. Hahn, 1997), expectations are usually defined as conscious processes that can be determined via self-reports (Kirsch, 1997). In the original form of the Expectancy Theory, expectancies shape one's voluntary behavior, whereas the placebo response usually refers to involuntary responses of the body. To bridge the gap, Kirsch has defined a special type of expectancy, the so-called response expectancy (Kirsch, 1997). Response expectancies reflect involuntary bodily responses (e.g., emotions, pain, sexual activation) and are self-reinforcing (or self-fulfilling) constructs. Very recently it was reported that mood stabilizers' relative efficacy in treating bipolar depression might be unrelated to the active drug response rates (Bartoli et al., 2018). Further, Szabo (2013) argued that part of the beneficial psychological effects of certain mood-enhancing interventions, like physical exercise (Szabo, Gaspar, and Abraham (2013), or deep-breathing (Szabo & Kocsis, 2016), may be attributed to positive expectations related to the outcome of the intervention. In other words, part of the responses may belong to the placebo phenomenon. However, the direct (non-medical) effect(s) of placebo agents on the acute affective states of healthy individuals were not examined to date.

Not all placebo interventions are equal (Kaptchuk et al., 2000). There are considerable differences in the perceived effectiveness of agents with various textures, colors, and shapes (Szabo, Bérdi, Köteles, & Bárdos, 2013). Different interventions evoke placebo responses in varying magnitudes (de Craen et al., 1996; Kaptchuk et al., 2006; Moerman, 2002). Placebos with characteristic taste, or well perceivable effect (or side effect), are called *active placebos* and can have stronger effects than the *pure placebos* (Miller & Colloca, 2009; Jospe, 1978), which contain only inert ingredients with no perceivable effects.

In trying out new leisure drugs surfacing in the form of a pill, like new psychoactive substances (NPS), people rely on the source and quality of the information available to them (Van Amsterdam, Nabben, Keiman, Haanschoten, & Korf, 2015). Information shapes people's expectancies, which in turn affects their behavior. It was found that when seeking information about NPS, and prior to using it, many youngsters (59%) relied on the Internet and their close friends (36%), while only few of them turned to doctors or family members (Eurobarometer, 2014). Although information is of key importance in forming expectancies, the *source* and/or *trustworthiness* of the information determines the strength of the expectancies (López & Sicilia, 2014)

Empirical evidence concerning the role of expectancies in shaping pain, anxiety, and depression-related placebo effects is substantial (Benedetti, 2009, 2011). However, much less is known about their impact on non-pathological conditions,

such as mood. Further, because psychoactive (i.e., affect-mediating) pills should theoretically be fast acting, measuring short duration (i.e., a few minutes) placebo effects may be important. However, the extant literature is void of such research. Recently, however, it was reported that information priming could trigger acute changes in affect after only three-minutes (Szabo & Kocsis, 2016). In this study we tested the acute—three-minute—psychological effects of an inert placebo "super pill" that was presented to participants as a new mood-enhancing agent able to enhance mood in only a few minutes while its ingredients are fully natural, harmless, and legal. To further strengthen the trustworthiness of the presented information (López & Sicilia, 2014), the participants were informed about the legitimate fact that the investigation was carried out with the approval of the local Research Ethics Committee responsible for the welfare of the research participants.

We selected an active placebo that is commonly known and, in general, may be associated with positive effects through sensory experience. Although the placebo effect is usually measured as the difference between a placebo and a non-treatment group, several other methodological options exist. For example, a correlation between *a priori* expectancies and the magnitude of the respective change, or a difference in outcome between two groups receiving different placebos also indicate that placebo (i.e., non-specific) mechanisms are at work (Benedetti, 2009; Moerman, 2002). Expectancies acquired by personal experience are usually stronger than those based on observation, information, and persuasion (Humphrey, 2002; Montgomery & Kirsch, 1997; Voudouris et al., 1990). Thus, we hypothesized that the "super pill" will induce positive psychological changes in a very short time (i.e. 3 minutes) in the pure placebo group through information-induced expectancy, while greater changes will be observed in the active placebo group, due to familiarity and/or pleasant past sensory experience with the agent.

Method

Participants

To avoid self-selection that, based on expectations, could alter the results of this type of work, two first-year undergraduate groups studying sports science were delivered a practical session as part of the course curriculum in which the psychological effects of a new mood-enhancing "super pill" (placebo) and a piece of *Tic Tac* (active placebo) were studied. Participants' mean (M) age was 19.94 ($SD = 2.58$) years; one-third of them were men. All were Caucasians who belonged to the upper middle social class. Despite the class-work nature of the research, since some participants had to ingest an unknown pill, ethical permission for the study was obtained from the Research Ethics Committee of the Faculty of Education and Psychology at ELTE Eötvös Loránd University. Participants could deny consent to participation and were free to withdraw from the study at any time, but they had to assist as passive observers, because all aspects of the research represented instructional material. Seven students in the pure placebo group did not wish to take the unknown pill and chose to act as observers, while one person in the active placebo group could not

take the *Tic Tac*, because she was on a sugar-restricted diet. A total of 80 participants started and completed the study, with 40 individuals in each group. At a later stage, after the data collection, all details of the research were discussed in the form of a lecture with the two groups of participants and its contents were part of a final examination in the course.

Materials

Questionnaires

The Positive and Negative Affect Schedule (PANAS – Watson, Clark, & Tellegen, 1988) was used for measuring affect before and following the pure placebo and active placebo interventions. In the current work we used the 10-item psychometrically validated Hungarian version of the instrument (Gyollai, Simor, Köteles, & Demetrovics, 2011; from Original English version: Thompson, 2007), which consists of five positive adjectives (i.e., active) and five negative items (i.e., nervous). The 10 adjectives are rated on a 5-point Likert scale ranging from 1 (*very slightly, or not at all*) to 5 (*very much*). An aggregate score can be obtained for both positive and negative items by summing up the respective ratings. The original PANAS was presented with excellent psychometric properties (Thompson, 2007; Watson et al., 1988). The internal consistencies of the Hungarian version (Gyollai et al., 2011) were (Cronbach's alpha) .73 for positive affect and .65 for negative affect, which are relatively low, but still acceptable.

To complement the information obtained with the PANAS, we have also employed a single-item (Andrews & Withey, 1976) 10-point Likert scale, ranging from 1 (*very bad*) to 10 (*very good*) to determine the level of the subjectively experienced momentary physical wellbeing before and after the interventions. Momentary wellbeing was conceptualized as "core affect" based on Russell's (2003) work. Core affect might be best described as the basic process of one's conscious psychophysiological state available as the simple non-reflective feeling, such as feeling good or bad, feeling lethargic, or energized (Russell, 2003). Another single-item 6-point Likert scale (ranging from *very negative* [1] to *very positive* [6]) was administered before the respective intervention to measure the expectation associated with the ingestion of mood-enhancing pill, or *Tic Tac*. Finally, another single-item 6-point Likert scale (ranging from *not at all* [1] to *very much* [6]) was presented immediately after the two interventions to assess the degree to which participants were convinced that the respective intervention was effective in changing their affective states and making them feel better. In other words, the perceived effectiveness of the intervention was measured using this item.

Ingested pills

Participants in the pure placebo group received a single placebo pill (a white, round pill, with a 7-mm diameter, manufactured by Winthrop Arzneimittel GmbH,

Mülhelm-Kärlich, Germany) with a glass of still mineral water. The pill contained lactose monohydrate, magnesium stearate, and cellulose. None of the participants were familiar with the pill, or its placebo nature. Participants in the active placebo group received a well-known commercially available *Tic Tac* mint, manufactured by Ferrerro Società per Azioni, Italy; its ingredients are: sugar, maltodextrin, tartaric acid, natural and artificial flavors, rice starch, gum arabic, filling agent (magnesium stearate), artificial colors, and a glazing agent (carnauba wax). All participants in this group were familiar with the *Tic Tac*, and had tasted it earlier.

Procedure

The experimental protocol is illustrated in Figure 1. Data collection took place in a group setting without any form of interaction between the participants. The pure placebo group received the information that new research has shown a new totally harmless pill made of natural ingredients is able to uplift people's mood in only 10 minutes; the scope of the current research is to determine whether these effects could be experienced after only three minutes (the detailed instructions are available from the authors upon request). The active placebo group was told that rewarding ourselves with a piece of mint, chocolate, or any sweets is a positive act. The aim of the current work is to examine whether the ingestion of a *Tic Tac* has any psychological benefits after 3 minutes following ingestion. Participants were informed about the ingredients of the pure placebo pill / *Tic Tac* and asked that those allergic, or possibly allergic, to any of the ingredients should refrain from participation in the study, but remain in the class as observers. Subsequently, after consent for participation, members of both groups were given the first set of questionnaires (serving the baseline/control measures) as well as the pure placebo pill with a cup of water or the *Tic Tac*. They were instructed that after completing the questionnaires the ingestion of the respective agent should occur at the same moment, when indicated by the experimenter, to allow the accurate measurement of the 3 minutes during which the anticipated effects may occur. Exactly three-minutes later, the participants completed the PANAS, reported their physical wellbeing, and rated the perceived effectiveness of the intervention.

Data analyses

One sample t-tests were used for manipulation check to determine whether expectancy (measured before treatment) and perceived effect (assessed three minutes later) differed from the median score. The three dependent variables (positive affect, negative affect and physical wellbeing) were analyzed with a 2×2 multivariate analysis of variance (MANOVA) to test the between-subject effect of group and the repeated measures effect of pre/post intervention testing. Follow-up univariate ANOVAs were calculated on each of the dependent variables when necessary. The relationships between expectancy scores, the three dependent measures, and perceived effect scores, were examined with correlations.

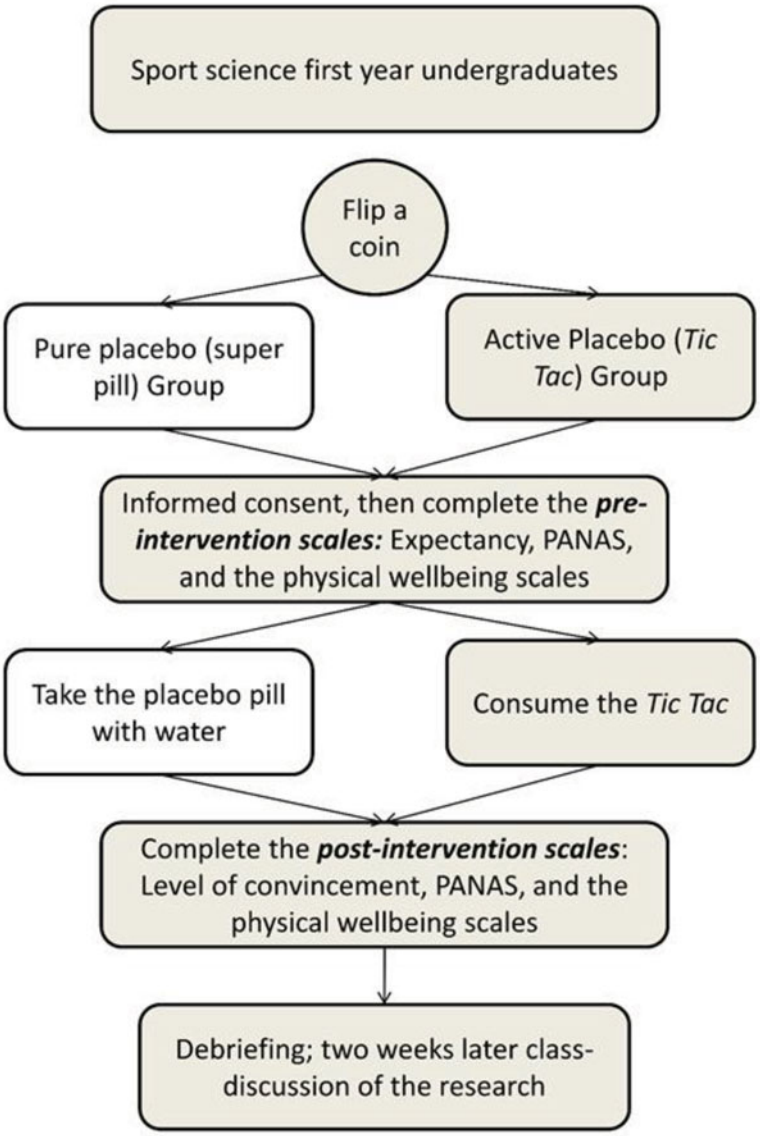

Figure 1. Flowchart of the experimental protocol.

Results

One-sample t-tests

The one-sample t-tests used for manipulation check revealed that the mean expectancy of positive effects were greater than the median-value of the rating scale ($Mdn = 3.5$) for both the pure placebo ($M = 4.24$, $SD = 0.48$; $t(39) = 9.83$, $p < .001$) and active placebo group ($M = 4.48$, $SD = 1.61$; $t(39) = 10.09$, $p < .001$). These values did not differ between the two groups ($p > .05$), showing that expectations related to the interventions were similar in the two groups.

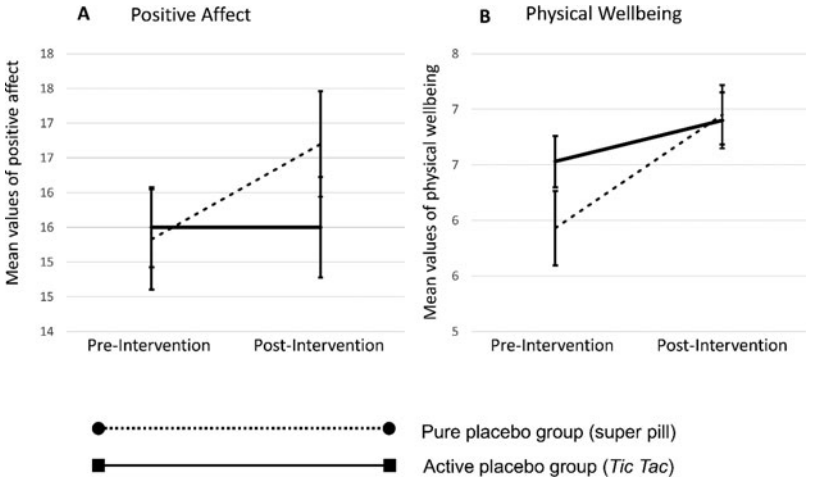

Figure 2. Statistically significant group by time interaction (A) in positive affect: increase noted in the active placebo group ($p < .001$), but not in the pure placebo group, and (B) in physical wellbeing: increase noted in both groups ($p = .012$ and $p < .001$). The increase in the Tic Tac group was greater than in the pure placebo group ($p = .022$). The figure presents the means and the standard errors of the means on relative scales for clearer visualization of the effects.

Main analysis

The 2 × 2 repeated measures MANOVA of the three dependent measures yielded a statistically significant time main effect, Pillai's trace = .404, $F(3,76) = 17.21$, $p < .001$, effect size (partial ETA squared [η^2_p]) = .404, and a group by time interaction, Pillai's trace = .132, $F(3,76) = 17.21$, $p < .001$, $\eta^2_p = .132$. The univariate tests revealed that the multivariate interaction was due to a statistically significant group by time interaction in positive affect, $F(1,78) = 6.74$, $p = .011$, $\eta^2_p = .080$, and in physical wellbeing, $F(1,78) = 8.42$, $p = .005$, $\eta^2_p = .097$. The interactions are illustrated in Figure 2. No significant group by time interaction emerged for negative affect ($p > .05$). However, a time main effect showed that negative affect decreased significantly from pre- to post-interventions ($M = 6.14$, $SD = 1.70$ vs. $M = 5.55$, $SD = 1.39$), regardless of group membership, $F(1,78) = 29.60$, $p < .001$, $\eta^2_p = .275$. The means (M) and standard deviations (SD) of the dependent measures are presented in Table 1.

Table 1. Means and standard deviations (in parentheses) of the dependent measures presented separately for the pure placebo and active placebo groups.

Measure	Pure Placebo Group	Active Placebo Group
Expectancy	4.2 (0.5)	4.5 (0.7)
Perceived Effect	3.3 (1.3)	3.8 (1.3)
Positive Affect Pre-Intervention	15.5 (3.7)	15.3 (4.6)
Positive Affect Post-Intervention	15.5 (4.6)	16.7 (4.8)
Negative Affect Pre-Intervention	6.0 (1.4)	6.3 (2.0)
Negative Affect Post Intervention	5.5 (1.1)	5.7 (1.6)
Physical Wellbeing Pre-Intervention	6.5 (1.5)	5.9 (2.1)
Physical Wellbeing Post-Intervention	6.9 (1.6)	7.0 (1.7)

Using Bonferroni correction, the statistically significant interactions were followed up with paired t-tests, which revealed that positive affect increased from pre- to post-intervention only in the active placebo (*Tic Tac*) group, $t(39) = -4.89$, $p < .001$, while physical wellbeing increased in both groups, pure placebo: $t(39) = -2.62$, $p < .012$, and active placebo: $t(39) = -5.91$, $p < .001$. However, the percent (%) increase in the active placebo group was greater ($M = 33.38$, $SD = 69.95$) than in the pure placebo group ($M = 6.87$, $SD = 16.08$), as revealed by an independent t-test, $t(78) = 2.34$, $p = .022$. The two groups did not differ ($p > .05$) in any of the measures at pre- and post-intervention (Figure 2).

Correlations

Pearson Product-Moment correlation analyses between the dependent measures and the expectancy values yielded no statistically significant correlations between the three dependent measures in the active placebo group ($p > .05$, in all instances), but the expectancy scores correlated with positive affect pre- and post-intervention, as well as with physical wellbeing post-intervention ($p < .05$; see Table 2) in the pure placebo group. A statistically significant positive relationship between expectancy of the treatment effects (measured before the interventions) and perceived effectiveness of the intervention (assessed three-minutes later) was also disclosed in both groups (placebo: $r = .406$, $r^2 = .165$, $p < .011$, and active placebo: $r = .621$, $r^2 = .386$, $p < .001$). While the r^2 (coefficient of determination reflecting the shared variance among the two variables) was more than twice as high in the active placebo than in the pure placebo group, the two correlations did not differ significantly as determined by using the Fisher *r*-to-*z* method, which was used to calculate the significance of the difference between two correlation coefficients.

Perceived effect

The perceived effect concerning the intervention's positive impact did not differ from the scale's median ($Mdn = 3.5$) as revealed by one sample t-test. However, the group differences approached, but did not reach, the conservative level (.05) of statistical significance, $t(78) = -1.77$, $p = .08$, $M = 3.28$, $SD = 1.33$ pure placebo group, and $M = 3.80$, $SD = 1.32$ active placebo group, as revealed by an independent t-test. While this difference could only be considered as a trend, the calculated effect size was close to a moderate value (Cohen's $d = -0.39$).

Discussion

In line with our hypothesis, the information-primed pure placebo group exhibited less psychological improvement within 3 minutes when compared to the active placebo group. Past research shows that information priming affects research outcomes (Bjørkedal & Flaten, 2011; De La Vega et al., 2017; Szabo & Kocsis, 2016; Webb, Hendricks, & Brandon, 2007). In contrast, the current results agree with the

Table 2. Correlations (r) between the repeated dependent measures, expectancy and perceived effect scores.

	Expectancy	Perceived Effect	Positive affect pre-	Positive affect post-	Negative affect pre-	Negative affect post-	Physical wellbeing pre-	Physical wellbeing post-
Expectancy		.406*	.417*	.352*	− .205	− .204	.198	.404*
Perceived Effect	*.621**		.295	.445*	− .288	− .271	.284	.404*
Positive affect pre-	*.113*	*.053*		.785*	− .113	− .112	.357*	.338*
Positive affect post-	*.203*	*.180*	*.929**		− .016	− .054	.212	.298
Negative affect pre-	*− .112*	*− .123*	*− .018*	*.041*		.774*	− .134	− .103
Negative affect post-	*− .132*	*− .250*	*.061*	*.039*	*.852**		− 115	− .145
Physical wellbeing pre-	*.167*	*.187*	*.582**	*.557**	*− .416**	*− .354**		.832*
Physical wellbeing post-	*.267*	*.453**	*.426**	*.496**	*− .390**	*− .458**	*.857**	

Note. The upper part of the table presents the r values for the pure placebo group, while the lower part (in italics) reflects the scores of the active placebo (Tic Tac) group.
*= statistically significant correlations $p < .05$.

findings of a recent inquiry in which the use of information priming did not mediate the placebo effect while experience did (Rosén, et al., 2016). Indeed, in the current work, the pure placebo group had no experience with the newly presented agent, while those in the active placebo group were familiar with the *Tic Tac*. The latter group also received positive, although not as strong or persuasive as the pure placebo group, information concerning the rewarding effects of a mint. This information, along with experience and pleasant sensation (the taste of mint), could have contributed to the positive changes in affect and physical wellbeing. The overall psychological effects were greater in the *Tic Tac* group than in the pure placebo (super pill) group, although expectancy scores did not differ between the two groups. It is known that tastes and smells can be easily conditioned (quite often only one experience is enough to develop an association). The consumption of a *Tic Tac* is a pleasant event, which can be associated with the characteristic taste. Moreover, tastes and smells can directly impact one's mood through the limbic system (Babulka, Berkes, Szemerszky, & Köteles, 2017; Dobetsberger & Buchbauer, 2011; Jellinek, 1997). Briefly, the pleasant sensory experience and expected positive mood state associated with the mint might have played a stronger role in altering affect and wellbeing than expectancies evoked by the information participants received. Thus, it appears that information versus earlier experience and positive sensory experience produce different outcomes as suggested in past works (e.g. Szabo & Kocsis, 2016).

It is possible that a certain level of doubt, or skepticism was also associated with the unknown pill. This factor, despite reassurances, could have interfered with both level of expectancy and the outcome. Indeed, the level of expectancy should have been higher in the pure placebo group versus the *Tic Tac*, but it was not the case. Further, while the *Tic Tac* group enjoyed a sensory pleasure during the brief study, the pure placebo group may have concentrated on the emergence of the suggested effects, that was not happening. However, if that was the case, it did not produce any negative feelings, since, despite the lack of increase in positive affect, a small increase in subjective physical wellbeing (refer to Figure 2) was seen in this group. Further, there was an overall decrease in negative affect independent of group membership. This result is difficult to explain, especially because participants had very low negative affect scores at the beginning. It may be linked to a Hawthorne effect but also to the ending of the compliance with the research requirements. Alternatively, since the study was performed in the class instead of a usual lecture, the novelty and the successful completion of the research requirements could have affected perceptions of negative affect.

It should be reiterated, that based on the design of the information-priming (providing a "super pill") we expected to induce expectancy in the pure placebo group that could translate into positive subjective psychological experiences. These effects were partly observed. The lack of more convincing evidence may be related to the unfamiliarity with the pill, doubt, or skepticism, surprise to conduct this kind of research in a university environment, which all could have contributed to the constrained effects. The doubt-skepticism explanation may be reinforced by the observed *trend* in a lower perceived effect of the intervention in the pure placebo

than active placebo group. This could be linked to the primed information provided to the participants that past studies showed an effect of the "super-pill" after 10 minutes, while the present inquiry tested whether similar effects would surface after only 3 minutes. Further, the stronger association between expectancy and perceived effect in the *Tic Tac* group versus the super pill group also suggests presumed skepticism, or uncertainty, about the pill's effect. Unfortunately, measuring perceived effect at the end of the intervention does not answer the question about thoughts and beliefs during the period after the ingestion of the "super pill," that could affect the outcome (Aikens, Nease, Nau, Klinkman, & Schwenk, 2005). Therefore, this variable should be assessed in future research to obtain a clearer explanation for the findings.

The fact that perceived effect did not differ from the median value showed that, on average, after the study participants exhibited a medium level of association between taking the pill or the mint and the affective responses. However, according to the *SD* values, there were substantial individual differences. Nevertheless, a relatively strong positive correlation was observed between participants' expectancies and the perceived effectiveness of the interventions. Concerning placebo and placebo-related effects, there is often a dissociation between objective (i.e. assessed using no self-report scales or assessed before and after the intervention) and subjective or perceived (i.e. assessed only after the intervention using self-report scales) effects (Babulka, Berkes, Szemerszky, & Köteles, 2017; Köteles & Babulka, 2014; Schwarz & Büchel, 2015). Expectancies usually have a greater impact on perceived effects than on the objective effects; in fact, they did not predict objective changes in many earlier studies (Babulka et al., 2017; Köteles & Babulka, 2014; Schwarz & Büchel, 2015; Szabo, Szemerszky, Dömötör, De la Vega, & Köteles, 2017; Szabo, Szemerszky, Dömötör, Gresits, & Köteles, 2017). In other words, *a priori* expectancies often bias perception in a self-fulfilling direction.

Strengths and limitations

One strength of the work is the method of participants-selections in attempting to rule out self-selection that could bias the expectancy-based studies. Another possible strength is the administration of a fictive "super pill" merely for *instant* mood effects, thus possibly mimicking the expectation associated with the consumption of NPS agents. However, the study is not without limitations. While comparing pure placebo- versus active-placebo effects in a very short time, both groups received positive, nevertheless slightly different, information, thus if expectancies would have been different (but were not), it would have been extremely difficult to untangle the changes due to intervention, expectancy, or both. Further, while both ingested agents were white in color, the shape of the round pure placebo pill (i.e. 7-mm tablet) taken with water differed from the known shape of a *Tic Tac* mint taken without water. Both shape and water drinking might have affected the outcome of the study. Future research should use pure and active placebos that are administered in an identical manner. Finally, the absence of an uninformed control group is another

shortcoming of the current work that should be taken into consideration in the design of future studies.

Conclusions

Despite certain limitations, the current study shows that the ingestion of an unknown pill, accompanied by reassuring positive instructions, yields lesser acute psychological effects than a commonly known mint, like the *Tic Tac*. Positive psychological effects of both active and pure placebos emerged in only 3 minutes, which is new information that may reveal how positive messages associated with a certain product, in addition to sensory experiences associated with that product, could have an instant rewarding effect to the individual. Similar studies using comparable agents with similar sensory characteristics are needed in the future. The current study also revealed that safety-reassurance and extremely positive information-priming, has little- or no effect on the ingestion of an unknown pill that may have relevance to certain drug, like NPS, prevention interventions. To fine tune this channel of research, future studies should manipulate the type of information (very positive / very negative) associated with the ingestion of an unknown pill in addition to employing identical agents with similar sensory and perceptual characteristics.

Funding

This research was supported by the Hungarian National Scientific Research Fund (K 109549 and K 124132).

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