Do we need to deceive to achieve within placebo analgesia: How does personality influence open-label placebo and deceptive placebo responding?

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Abstract

Objective: Research has suggested open-label placebos are effective, however, there is a lack of research comparing the effectiveness of an open-label placebo (OLP) with a deceptive placebo (DP), although one study did find an OLP and DP were equally as effective for reducing pain. Furthermore, there is a gap within the literature investigating the influence of personality within OLP responding. This study aimed to compare the effectiveness of an OLP to a DP and investigated the role of personality within OLP analgesia.

Method: 75 participants were allocated to one of three groups; OLP (n = 25), DP (n = 26) and no-treatment (NT; n = 24). All participants completed a baseline cold pressor test (CPT) and measures of pain tolerance and pain intensity. Participants in the OLP group were informed they were receiving a placebo and participants in the DP group were informed they were receiving a painkiller. Those in the OLP and DP groups then received a placebo nasal spray, with the NT group receiving no placebo. All participants then completed a second CPT and the pain measures. Several personality-related variables were also measured.

Results: A one-way ANCOVA revealed no significant differences between groups for pain tolerance, $F(2, 71) = 1.903$, $p = .157$. However, significant differences were revealed between groups for self-reported pain intensity, $F(2, 71) = 4.838$, $p = .011$, $\eta^2 = .120$. Planned contrasts revealed that receiving an OLP and a DP significantly decreased pain intensity compared to the NT group, with no significant differences between the effectiveness of the OLP and the DP. Exploratory analysis, using moderated regression analysis, revealed fear of minor pain was positively associated with placebo analgesia within the OLP group. Fear of medical pain was positively associated with pain intensity for those in the OLP group, however, there was a negative association for those in the DP group. There was a positive association between pain intensity and agreeableness for those in the DP group, however, a negative association for those in the OLP group.

Conclusion: An OLP and a DP were both effective for reducing subjective pain intensity, although there were no significant differences between OLP and DP effectiveness. This suggests the use of deception within placebo analgesia should be questioned with healthy participants, as placebos given openly remained as effective as placebos given deceptively. This was also the first study to highlight that agreeableness, fear of minor pain, and fear of medical pain moderated OLP analgesia in a differing direction to DP analgesia.

Keywords: open-label placebo, placebo analgesia, personality-related variables, pain

Common Abbreviations

OLP - Open-Label placebo

DP - Deceptive placebo

NT - No treatment

CPT - Cold Pressor Test

Contents

1. Introduction

The use of placebos is well documented within medical practice (Charlesworth et al. 2017); however, placebos have been argued to be unethical, given medical professionals are required to deceive patients about the true nature of a placebo (Petkovic et al., 2015; Fässler, Meissner, Schneider, & Linde, 2010). Despite the argument, it was reported that, within the UK, 12% of General Practitioners (GPs) used a pure placebo (placebo with no pharmacologically active ingredients such as a sugar pill) within their career. It was also found that 97% of GPs used an impure placebo (a substance or intervention with some known clinical or physical value, however lacking specific therapeutic effects such as off-label uses of potentially effective therapies) at least once within their career (Howick et al. 2013). Although the use of placebos is well documented, the level of effectiveness of placebos is inconsistent within research (Howe, Goyer, and Crum 2017). Furthermore, suggestions have been made that the placebo effect is more effective in patients compared to healthy individuals (Forsberg, Martinussen, and Flaten 2017), suggesting placebo research using healthy participants may underestimate the effectiveness of placebos when compared to a clinical sample.

Placebos have been found to be effective for reducing pain, otherwise known as placebo analgesia, within healthy participants (Bąbel et al. 2017; Geers et al. 2015; Rosén et al. 2017) and within clinical samples with those suffering from lower back pain and chronic pain (Charron, Rainville, and Marchand 2006; Müller et al. 2016). In addition, placebos have also been used to reduce symptoms for various other medical conditions, including psychological disorders such as depression (Walsh et al. 2002) and schizophrenia (Kinon, Potts, and Watson 2011). A meta-analysis has also indicated that placebo surgeries, for conditions such as severe obesity and gastro-oesophageal reflux, relieve symptoms in 75% of cases, with there being no significant difference between the effectiveness of a placebo surgery and a genuine surgery within over half of the cases analysed (Wartolowska et al. 2014). Furthermore, it is often suggested that placebo effects are only relevant with subjective outcomes, such as patient-reported pain (Breidert and Hofbauer 2009; Hróbjartsson and Gøtzsche 2001; Kaptchuk and Miller 2015), usually only relieving symptoms and side effects, opposed to curing illnesses (Kaptchuk and Miller 2015). However, there is some evidence that placebo effects can influence objective outcomes, such as decreasing a rash size from a histamine skin prick test (Howe et al. 2017) and influencing plasma ghrelin levels within female participants' blood (Hoffmann et al. 2018).

Until recently, it was believed that for placebo effects to occur, deception was necessary (Kaptchuk, 2018; Leibowitz, Hardebeck, Goyer, & Crum, 2019). In other words, for an individual to experience a placebo effect, they were required to believe that the placebo they received was a genuine drug with active ingredients. However, given the long-standing belief that placebos require deception, the use of placebos within medical practice has been argued to be unethical (Charlesworth et al. 2017; Colloca and Howick 2018). Thus, Kaptchuk et al. (2010) suggested that finding effective ways of harnessing the placebo effect without deception should be of high priority. In recent years, research has questioned whether deception is a necessary component within the placebo effect, by prescribing placebos without deception, referred to as an open-label placebo (OLP). Thus, an OLP is a placebo prescribed where a patient has the knowledge and understanding that it is a placebo containing no active ingredients.

1.1. Open-label placebos

Open-label placebos have been documented to elicit placebo analgesia within clinical samples suffering from chronic lower back pain and episodic migraine attacks (Carvalho et al., 2016; Kam-Hansen et al., 2014). OLP effects have also been demonstrated and have shown some effectiveness when reducing symptoms for various other medical conditions; Attention Deficit Hyperactivity Disorder (ADHD; Sandler & Bodfish, 2008), Irritable Bowel Syndrome (IBS; Kaptchuk et al., 2010), cancer-related fatigue (Hoenemeyer et al. 2018; Zhou et al. 2019) depression (Kelley et al. 2012), and allergic rhinitis (Schaefer, Harke, and Denke 2016; Schaefer, Sahin, and Berstecher 2018).

Placebos without deception have mostly only focussed on clinical samples, however, there is a limited amount of research with healthy participants, some of which is inconsistent (Barnes et al. 2019; El Brihi, Horne, and Faasse 2019; Locher et al. 2017; Mathur et al. 2018; Meeuwis et al. 2018). Some studies using healthy participants have found positive OLP effects such as improving wellbeing and sleep quality, and reducing the level of itch individuals expected after receiving a histamine iontophoresis (El Brihi et al. 2019; Meeuwis et al. 2018). However, Barnes et al. (2019) found that an OLP was not useful for reducing experimentally induced nausea using brain stimulation as a placebo. It must be said, however, that these studies investigated different effects and utilised different placebos with El Brihi et al. (2019) using placebo pills and Meeuwis et al. (2018) using verbal suggestions. A further OLP effect was highlighted by Locher et al. (2017), whereby receiving a placebo cream with a persuasive rationale decreased subjective pain intensity and unpleasantness ratings. On

the other hand, it was found that there were no OLP effects within objective pain tolerance (Locher et al. 2017). This is also in line with Mathur et al. (2018) whereby it was demonstrated that an OLP did not influence wound healing, an objective outcome.

A limitation within the current OLP literature is that the 'control' group used in the above studies is not consistent, with some studies using a no-treatment group (Kaptchuk et al. 2010; Sandler and Bodfish 2008), and others using a 'treatment as usual' group as the comparison group (Carvalho et al. 2016). This, however, does raise the question whether the full extent of an OLP effect can be highlighted if a control group continues to experience other treatment. In addition, the majority of OLP studies only compare an OLP with a control group, without being compared to a deceptive placebo (DP) group, a group whereby participants believe the placebo to be an active drug. This, therefore, suggests that research comparing an OLP with a control group only has the potential of suggesting an OLP is effective compared to those who have not received any placebo. However, without a DP group being included in the same studies, it can only be possible to confirm that an OLP is effective to some extent, without knowing how effective it is compared to a DP.

Although there is a lack of research comparing the effectiveness of an OLP with a DP, there are a small number of studies which have compared their effectiveness (Barnes et al., 2019; Locher et al., 2017). Locher et al. (2017) compared two OLP groups, one with and one without a plausible rationale, a DP group, and a no-treatment group within a laboratory study measuring objective pain tolerance, and subjective pain intensity and unpleasantness ratings within a heat pain test. It was found that there were no group differences for objective pain tolerance, with all placebo groups showing no placebo analgesia. However, regarding subjective ratings of pain, the OLP group with a rationale to increase expectation of pain relief and the DP group, did not significantly differ in terms of effectiveness, with an OLP group and DP group experiencing less pain than those in the OLP group without a rationale to increase expectation. This suggests that, on the condition that an OLP is given with a plausible rationale consisting of several statements to increase expectancy of pain relief from a placebo, it remains equally as effective as a DP; questioning the relevance of deception within placebo analgesia. A further study compared an OLP and DP within healthy participants to investigate whether it was possible to reduce experimentally induced nausea (Barnes et al. 2019). Two experiments were conducted utilising two different methods of modelling nausea and two different types of placebos. It was found that when using Galvanic Vestibular Stimulation to model nausea and a peppermint vapour as a placebo, there were no significant placebo effects for the OLP or DP groups. However, when using

Virtual Reality to induce nausea and brain stimulation as a placebo, there were significant placebo effects for the DP group, however, not for the OLP group. Although Barnes et al. (2019) contradicts the findings of Locher et al. (2017) it is important to understand that both studies focus on different outcomes, however, Barnes et al. (2019) also suggested that other characteristics are likely to be involved with the likelihood of responding to a placebo such as the type of placebo used.

1.2. Expectancy and conditioning theories

Two dominant theories which seek to explain the placebo effect are expectancy and classical conditioning (Stewart-Williams and Podd 2004). Expectancy theory refers to the concept that individuals experience a relief in symptoms because they expect it, with the expectation of relief creating a placebo effect (Stewart-Williams and Podd 2004). Conditioning has also been argued to explain the placebo effect, for example, taking the classical conditioning concept of repeatedly pairing a neutral stimuli (NS) with an unconditioned stimuli (US, which creates an unconditioned response, UR), the NS becomes conditioned to create the same response as the US, thus, becoming a conditioned stimuli (CS) to create a conditioned response (CR). To explain this in terms of the placebo effect, a drug may be an US which leads to an UR, for example pain relief. By administering a NS such as a pill case, containing an US (such as a painkiller) which creates an UR (such as pain relief), the painkiller is repeatedly paired with the method of administration of the drug; in this case a pill case. Through repeated pairing of the NS and the US, the pill case could become associated with pain relief, without the painkilling ingredient being inside the pill case. Thus, a placebo is the CS and the placebo effect is a CR (Stewart-Williams and Podd 2004).

Although expectancy theory has been suggested to be a key theory, Kaptchuk (2018) has suggested that it assumes recipients have positive experiences with treatment, however, he suggested that patients, in fact, do not hold positive expectations towards treatments. Furthermore, clinical evidence is inconsistent for the role of expectancy within the placebo effect (Kaptchuk 2018). When specifically investigating the role of expectancy for the OLP, research is also inconsistent as it has previously been found that expectations did not influence the efficacy of an OLP in one study (Schaefer et al. 2018). However, it has also been found that, by raising expectation through a positive rationale, expectation does increase the effectiveness of an OLP (Locher et al. 2017). Classical conditioning also relies on positive previous experience, otherwise positive placebo outcomes would not be experienced. Furthermore, given there is often frequent history of medical failure, with individuals not responding

positively to previous medical interventions, Kaptchuk (2018) has claimed conditioning is unlikely to be major factor when explaining the OLP.

With regards to this study, we assume that expectation may hold greater merit when explaining OLP analgesia within a healthy sample for the following reasons. The study which is most similar to this current study in terms of methodology and aims, Locher et al. (2017), found that when an OLP was given with a rationale to increase expectation of pain relief, it was more effective than an OLP given without a rationale. This suggested that the role of expectation may hold importance within OLP analgesia and, therefore, this current study takes into consideration the findings and the potential usefulness of the role of expectation when increasing the effectiveness of an OLP. When taking into account the role conditioning may have within OLP studies containing healthy participants such as this study, if conditioning were to be the underlying mechanism explaining an OLP, it would be assumed that all participants who experiences a placebo effect would have previous experience with the placebo in a genuine medication form. For example, given Locher et al. (2017) used a placebo analgesic cream, for conditioning to be an underlying mechanism explaining how a placebo cream given openly reduced pain, it would have to be the case for all participants who experienced a reduction in pain to have previously experienced pain relief from a genuine analgesic cream. It is, however, unlikely that all participants had previous exposure to an analgesic cream, and therefore unlikely that conditioning was an underlying mechanism. Thus, given expectancy has been demonstrated to be somewhat useful when increasing the effectiveness of an OLP, and it is unlikely for all participants to have had previous exposure with the placebo form as a genuine medication, this study assumes that expectancy is more likely to play a greater role within placebo analgesia. Finally, although conditioning and expectancy theories appear to be most dominant within placebo literature, it could be the case that there are further mechanisms, or an interaction of mechanisms, which lead to OLP effectiveness.

1.3. Personality and deceptive placebo responding

Research has also indicated that personality may have some influence on placebo responding, although the role of personality within placebo responding presents itself as ambiguous, and research is both limited and presents inconsistencies.

1.3.1. Optimism

Optimism appears to be one of the most consistent predictors of placebo responding (Geers et al., 2005, 2007, 2010; Locher et al., 2019; Morton et al., 2009), although there are also inconsistencies within the literature highlighting that optimism does not influence placebo responding (Peciña et al. 2013; Vachon-Presseau et al. 2018).

When understanding the reasons why optimism may predict placebo responding, Maltby et al. (2010) suggested that those who are more optimistic usually expect positive outcomes, meaning optimists are more likely to work towards achieving goals and not giving up in the process. On the contrary, Maltby et al. (2010) stated the opposite for pessimists, with pessimists more likely to expect negative outcomes, meaning they are more likely to give up on achieving their goals. When applying this to the placebo effect, optimists may be more likely to expect a positive outcome from a placebo, such as pain relief or a reduction in symptoms, and in the process, they do end up experiencing greater benefits from a placebo. Pessimists, however, may be less likely to experience a placebo effect as they may not expect the placebo to be effective and, consequently, they may not experience the benefit from the placebo that a more positive thinker may experience. Thus, it is possible to speculate that the role expectancy plays within the placebo effect may be similar to the role optimism plays as optimism and expectancy appear to be closely related mechanisms.

1.3.2. Big 5

Although optimism appears to be the most consistent personality-related predictor of placebo responding (Locher et al. 2019), elements of the Big 5 have also been suggested to predict placebo responding; extraversion (Kelley et al. 2009), agreeableness (Kelley et al. 2009; Peciña et al. 2013), openness (Kelley et al. 2009; Vachon-Presseau et al. 2018), and neuroticism has been found to be a negative predictor of placebo responding (Peciña et al. 2013).

When understanding the role agreeableness may play within placebo responding, it has been stated that those who score higher on agreeableness are more trusting, however, those who score lower are usually more sceptical (Maltby et al., 2010). Thus, this suggests that those who are more trusting may be more trusting that a placebo will be effective, although those who

score lower on agreeableness may be more sceptical about whether the placebo will be effective, potentially decreasing its effectiveness. Furthermore, Quilty et al. (cited in Peciña et al., 2013) stated that those who score high on agreeableness are likely to have a stronger patient-doctor relationship and, therefore, are more likely to engage within therapy.

Extraversion was revealed to be the most robust predictor of placebo responding within the findings of Kelly et al. (2009), suggesting that those who are sociable, assertive and optimistic are more likely to experience a placebo effect (Maltby et al., 2010). Furthermore, with previous research finding neuroticism to be a negative predictor of placebo responding (Peciña et al., 2013), this suggests those who are calmer and more emotionally adjusted are more likely to experience a placebo effect (Maltby et al., 2010). Thus, those who are emotionally unstable are less likely to experience a placebo effect. Finally, with openness also being a predictor of placebo responding, it is highly likely that the explanation is as follows; those who are more open to new experiences are also more open to a new form of medication and, therefore, are more likely to experience the effects of a placebo.

1.3.3. Behavioural activation systems

Two elements from the BIS/BAS scales (Carver & White, 1994) have also been found to be associated with placebo responding; BAS drive and BAS fun seeking (Darragh, Booth, and Consedine, 2014; Schweinhardt et al., 2009), however, studies have contradicted each other. When research was conducted on the placebo effect within pain (Schweinhardt et al., 2009), BAS drive and BAS fun seeking were identified to positively predict placebo responding, however, in a non-pain context the same traits were negatively associated with placebo responding (Darragh et al., 2014). It has, therefore, been suggested that the influence of personality on placebo responding, specifically BAS drive and BAS fun-seeking, may differ within pain and non-pain contexts (Darragh et al. 2014). Furthermore, given research has highlighted this inconsistency and the influence of behavioural drive and fun-seeking is not fully established, further research should be conducted to further uncover the relationships between behavioural activation systems and placebo responding.

1.3.4. Fear of pain

Fear of pain has also been identified to reduce placebo responding with both dispositional fear (Lyby, Aslaksen, and Flaten, 2010, 2011) and induced fear (Lyby et al., 2012). More specifically, those who fear severe pain are less likely to respond to a placebo (Lyby et al., 2010). Thus, those who fear pain are less likely to experience a placebo effect. When seeking an explanation for this, Lyby et al. (2010) found that fear of pain was also related to stress during pain and in the anticipation of pain, suggesting those who are more stressed are more likely to fear pain and, consequently, less likely to experience a placebo effect.

1.3.5. Interactional approach

Although there are various examples where personality has been found to influence the likelihood of responding to a placebo, it has been suggested that, rather than there being a specific placebo personality, placebo responding may be explained by an interaction between dispositional and contextual factors (Darragh et al., 2014). Darragh, Booth, and Consedine (2015) referred to this as a transactional model. To further explain this, it has been suggested that dispositional factors, such as personality, interact with situational factors, such as the environment (Jakšić, Aukst-Margetić, & Jakovljević, 2013), with the strength and direction of the relationship between personality and placebo responsiveness being affected by situational variables. For example, the role of behavioural drive and fun-seeking may vary between contexts such as within pain contexts and non-pain contexts (Darragh et al., 2014; Schweinhardt et al., 2009).

Another example of an interaction is where pessimists were more likely than optimists to experience negative placebo effects, following a negative expectation stating a placebo would make them feel unpleasant (Geers et al., 2005). Furthermore, Geers et al. (2007) found that optimistic people were more likely to experience a placebo effect when given a positive placebo expectation. Thus, this suggests that, although optimism and pessimism play some role in predicting placebo responding, this is only relevant within particular contexts; such as receiving a positive or negative expectation. Research has also indicated an interactional approach with extraversion and agreeableness, with those who scored higher on extraversion and agreeableness responding more effectively with an empathic clinician (Kelley et al. 2009). This, therefore, suggests that dispositional extraversion and agreeableness interact with the

contextual factor of the characteristics of the clinician. Through understanding an individual's personality and the most suitable context it, therefore, may be possible to match individuals to placebo treatments which are most likely to be effective (Darragh et al. 2015).

1.4. Personality and open-label placebo responding

Although personality has been investigated in many studies with the DP, to date, there has been only one study which investigated personality with regards to the OLP (Locher et al. 2019). Locher et al. (2019) conducted a study investigating whether personality predicts OLP responding with healthy participants experiencing experimentally induced heat pain. Several personality-related variables were measured including; optimism, openness to experience, locus of control, and positive attitudes towards alternative and complementary medicine. Although optimism predicted DP responding, it was found that optimism did not predict OLP responding. Moreover, no other personality-related variables predicted OLP responding, suggesting that there is no typical 'OLP responder' personality. However, although this was the only study to research personality and OLP responding, there are several other personality-related variables suggested to predict DP responding in the DP literature which Locher et al. (2019) did not address. This, therefore, suggests that there may be personality traits predicting DP responding which may also predict OLP responding, which have not yet been researched. Thus, it is important to conduct further studies into the role of personality within OLP responding.

1.5. Rationale

Although OLPs have been found to be effective within some instances, there is a limited amount of research comparing OLP's with DPs. Furthermore, of the two known studies which have compared OLPs and DPs, Locher et al. (2017) and Barnes et al. (2019) found conflicting findings, although both studies were investigating unrelated outcomes. With a very limited amount of research comparing placebos given openly and deceptively and inconsistencies present in that pre-existing literature, it is important to conduct further research to understand the role which deception does play within the placebo effect. Through conducting research of this kind and understanding the relevance of deception within the placebo effect, only then can the potential of the use of OLPs within the real world be explored. It is, therefore, important to understand how the effectiveness of an OLP and DP compare to understand whether placebos can be given in a more ethical way, without deception, whilst ensuring effectiveness.

Given the lack of research comparing the role of personality within OLP responding, it is important that further research is conducted to both understand whether personality does influence OLP responding and whether personality influences OLP and DP responding in the same way. Given there is some research investigating the role of personality within DP responding, although limited, it suggests that personality may have some influence over the likelihood of responding to a placebo and, therefore, it is important to know whether the same personality traits influence OLP responding as this could suggest similar mechanisms may explain OLP and DP responding. Furthermore, if different personality-related variables were found to predict OLP and DP responding, this could have a potentially useful implication of using personality testing to match an individual to the best form of treatment, a placebo given openly or a placebo given deceptively. Furthermore, given little is known about the mechanisms explaining the OLP effect, understanding the role personality plays within OLP responding may be useful for understanding how and why the OLP could be effective.

Given this research was exploratory and there is very little research understanding the role of personality within OLP responding, it was important to measure personality traits which have been found to be effective for predicting DP responding as a basis as to what personality traits may also influence OLP responding. Furthermore, given questionnaires measuring personality traits which have been found to predict placebo responding also measure other personality traits, and this research was exploratory, the full questionnaires were given to participants. Thus, this meant that personality traits which have been suggested to influence DP responding were measured within this study, however, other personality traits were also measured as they may also influence OLP responding.

1.6. This study

The current study seeks to investigate two key questions. Firstly, are open-label placebos effective compared to a no-placebo control group within a cold-pressor test and, if so, how does their effectiveness compare to deceptive placebos? Secondly, do personality-related variables influence open-label placebos and, if so, is the relationship the same as with deceptive placebos? Therefore, we firstly hypothesised that OLP and DP groups will experience enhanced placebo analgesia (increased pain tolerance and decreased pain intensity) within a cold-pressor test compared to a no-treatment (NT) control group. Secondly, we investigated whether there were any differences between the effectiveness of an OLP and a DP within placebo analgesia. Finally, given there is little research investigating personality in relation to the OLP, exploratory analysis was performed to investigate whether personality traits influence OLP analgesia and how this compares to the influence on DP analgesia.

2. Method

2.1. Participants

Using an opportunity sampling method, 104 participants were recruited from the University of Huddersfield's Psychology department. However, several participants were excluded for reaching or being very close to the ceiling immersion time of 180 seconds within the baseline cold pressor test (CPT). See Appendix 1 for the histogram demonstrating the ceiling effect. As demonstrated by the histogram, there is a slightly skewed normal distribution between 0 seconds and 109 seconds, within the baseline CPT immersion times. However, no participants immersed their hands for a time period between 109 seconds and 162 seconds, with 4 participants immersing their hands for a time period between 162 and 178 seconds, and 25 participants immersing their hand for the full-time period permitted. This, therefore, meant that by removing those who were affected by the ceiling time from data analysis, there was a relatively normal distribution, although slightly skewed. More importantly, given an immersion time of 180 seconds meant that participants pain tolerance was higher than we were able to test, it was not possible to indicate whether a placebo effect had taken place or not when comparing the baseline CPT to the post-treatment CPT.

Therefore, only 75 participants were included within data analysis. 87% of participants were female (n = 65) and 13% were male (n = 10), with an age ranging between 18 and 54 (mean = 21.05, SD = 5.042). Participants participated in one of three groups; OLP (n = 25), DP (n = 26) and NT (n = 24). Participants were randomised into the OLP and NT group, however, given recruitment for the DP occurred at a later date, participants were not randomly assigned to this group; thus, any participants who volunteered to participate in the DP condition believed they were taking part in a study which investigated individual differences within painkiller responding. All groups consisted of a greater number of females; OLP group (76%), DP group (96%) and NT group (87.5%) and all other characteristics remained similar across all three groups.

2.2. Design

A 3 x 2 mixed factorial design was used. The between-subjects factor was experimental condition which had three groups; OLP, DP and the NT. The within-subjects factor was CPT trial with two levels; baseline CPT and post-treatment CPT. There were two dependent variables measuring pain perception; objective pain tolerance and subjective pain intensity. Objective pain tolerance was the CPT immersion time in seconds. Subjective pain intensity was measured using a digital visual analogue

scale ranging from 0 to 100, with 0 representing no pain and 100 representing the most intense pain imaginable. Various personality-related variables were also measured throughout this study.

As previous research has demonstrated there are large individual differences in pain perception (Rutchick and Slepian 2013), it was important to measure participant's pain perception before being given a placebo; ensuring any differences between the three groups were because of the administration of a placebo and not genuine differences in participant's pain perception. Thus, a pre-test post-test design was utilised with participants completing a baseline CPT before being given any stimuli which may influence pain perception. Furthermore, consumption of painkillers before participating in pain research may influence pain perception, suggesting it was important to screen participants for recent painkiller use to ensure there were no differences within painkiller usage between groups (Rutchick and Slepian 2013). Moreover, participants were screened for medical conditions which may influence their pain perception. Any participants who suffered from any listed medical conditions did not participate; acute or chronic pain, cardiovascular problems, arthritis, diabetes, fibromyalgia, Reynaud's Disease, or if participants were allergic to sodium chloride.

2.3. Materials and Apparatus

Participant Booklet

Participants were given a paper booklet which consisted of an information sheet, consent form and debrief sheet. In addition, the booklet included questions for a reading comprehension task given in a separate booklet and a placebo information sheet or painkiller information sheet was included for those in the OLP and DP groups.

Online Materials

Qualtrics, an online survey platform, was used to collect data and inform participants about their tasks throughout the study and was displayed on a computer screen within the laboratory. Participants followed instructions on the computer screen throughout the research process with limited researcher-participant interaction. Qualtrics was also used to collect responses to all psychometric measures within this study. Qualtrics follows the US, EU and Swiss Safe Harbor Framework regarding the collection, use and retention of personal data.

Demographic questionnaire

Basic demographic information was collected from each participant, including; gender, age and marital status. Furthermore, at the end of this questionnaire, participants were screened for the use of painkillers within the last four hours. Participants were informed on all recruitment materials that they should not take painkillers within the 4 hours prior to them taking part in this research to control for the influence of painkillers on participant's pain perception (Rutchick and Slepian 2013).

Information provided to the OLP condition

Participants in the OLP group were given a placebo information sheet. The information sheet included basic instructions to familiarise participants with the method of administrating the placebo. Furthermore, this information sheet included several statements with the purpose of increasing the expectation of pain relief from administering a placebo (Locher et al. 2017). Firstly, participants were informed that the nasal spray is inactive and does not contain any painkilling properties. Participants were also informed that, although they are administering a placebo, they may still experience pain relief, given previous research has demonstrated that placebos can reduce symptoms and reduce pain when participants have an understanding that they have administered a placebo. Moreover, the placebo information sheet informed participants that having a positive attitude towards the placebo can improve its effectiveness, however, a positive attitude is not necessary. Research has suggested that raising expectation of pain relief from a placebo is a useful way of increasing the effectiveness of an OLP (Locher et al., 2017). This study replicated two key pieces of information from Locher et al. (2017) to increase expectation of pain relief regarding the effectiveness of open-label placebos, and that a positive attitude can be helpful, however, not necessary. *See Appendix 2.*

Information provided to the DP condition

Participants in the DP condition were given a painkiller information sheet. Alike to the placebo information sheet, information was given explaining how to administer the nasal spray. The information followed a similar format to that used in previous research (Locher et al., 2017). Participants were informed that they were receiving an analgesic nasal spray, containing Lidocaine, the main ingredient used in Stilex (a painkiller used in Switzerland). The information sheet stated that Lidocaine provides pain relief for a short period of time, providing relief from medical procedures and for chronic pain. It was also suggested that the effectiveness of the painkiller had been tested in studies worldwide. Finally, participants were informed that Lidocaine takes approximately 30 seconds

to induce an analgesic effect. Although this explanation was inspired by Locher et al. (2017), there have been some adaptations including changing the description to suit a nasal spray, as opposed to an analgesic cream. *See Appendix 3.*

Big Five Inventory- 2 (BFI-2; Soto & John, 2017)

The BFI-2 is a developed version of the Big Five Inventory (BFI) measuring extraversion, agreeableness, conscientiousness, negative emotionality and open-mindedness. It includes 60 items rated on a Likert scale; disagree strongly, disagree a little, neutral; no opinion, agree a little, and agree strongly. Each personality trait is measured by 12 items. Each personality trait had a score ranging from 12 to 60, with higher scores representing more demonstration of the personality trait. The BFI-2 is a reliable and valid measure of said personality traits, with the five measured traits correlating with other established personality measures; BFI, Big Five Aspect Scales (DeYoung, Quilty, and Peterson 2007), Big Five Mini-Markers (Saucier 1994), NEO Five-Factor Inventory (NEO-FFI; McCrae & Costa, cited in Soto & John, 2017) and NEO Personality Inventory-Revised (NEO PI-R; McCrae & Costa, cited in Soto & John, 2017). Cronbach's alpha for this sample is as follows; extraversion ($\alpha = .84$), agreeableness ($\alpha = .71$), conscientiousness ($\alpha = .82$), negative emotionality ($\alpha = .91$) and open-mindedness ($\alpha = .84$).

Fear of Pain Questionnaire-III (FPQ-III; McNeil & Rainwater, 1998)

The FPQ-III is a 30-item questionnaire which measures the level of fear or anxiety felt towards various painful stimuli. Answers are recorded on a 5-point Likert scale; not at all, a little, a fair amount, very much and extreme. The possible range of scores for fear of pain is between 30 and 150, with higher scores representing more fear of pain and can be used with both a clinical and healthy population. There are three subscales within the FPQ-III, each with 10 items; fear of minor pain, fear of severe pain and fear of medical pain. The range of scores for each subscale is between 10 and 50. The FPQ-III has good construct, concurrent and ecological validity (Hursey & Jacks, cited in McNeil & Rainwater, 1998). There is good internal consistency within this sample; fear of pain ($\alpha = .91$), fear of severe pain ($\alpha = .88$), fear of minor pain ($\alpha = .84$) and fear of medical pain ($\alpha = .87$).

Behavioural inhibition system/Behavioural activation system scales (BIS/BAS scales; Carver & White, 1994)

The BIS/BAS scales are a 24-item questionnaire measuring 4 sub-scales. One subscale measures the BIS (7 items) with the other three subscales relating to the BAS; BAS drive (4 items), BAS reward responsiveness (4 items) and BAS fun seeking (5 items). Answers are given on a four-point Likert scale; very true for me, somewhat true for me, somewhat false for me, very false for me. The range of scores for the BIS is between 7 and 28. For BAS drive and BAS reward responsiveness, the range of scores is between 4 and 16, and between 5 and 20 for BAS fun-seeking. The BIS/BAS scales have good validity and test-retest correlations demonstrate a reasonable level of reliability (Carver et al. 1994). Cronbach's alpha within this sample is as follows; BAS drive (α = .69), BAS fun seeking (α = .68), BAS reward responsiveness (α = .62) and BIS (α = .86).

Life orientation test-revised (LOT-R; Scheier, Carver, & Bridges, 1994)

The LOT-R is a 10-item questionnaire, measuring dispositional optimism, with three items measuring optimism, three items measuring pessimism and four items performing the role of filler items. All items are rated on a five-point Likert scale; I agree a lot, I agree a little, I neither agree nor disagree, I disagree a little and I disagree a lot. The range of scores within the LOT-R is 0 to 24. The LOT-R has a good level of test-retest reliability, internal consistency and validity (Scheier et al. 1994). There was good internal consistency within the sample used in this study (α = .79).

Saline nasal spray

The placebo used in this study was the Boots Pharmaceuticals Saline Nasal Spray (15ml) with the advertised medical relief of nasal congestion for babies, infants and children. The nasal spray contained no active or painkilling ingredients. The ingredients are as follows; an isotonic buffered, aqueous saline solution containing sodium chloride 0.75%, 0.01% EDTA, 0.0002% PHMB. Nasal sprays were disposed of after each use. There are no known side effects of this product, however, online documentation suggests that, although very rare, individuals should seek urgent medical advice if they believe they are experiencing an allergic reaction to the nasal spray (WebMD, 2019).

Cold Pressor Test (CPT)

The cold-water bath used within this study was the Lab Companion, Jeio Tech refrigerating bath circulator, maintained at three degrees Celsius. The maximum immersion time for all participants was 180 seconds (Rutchick & Slepian, 2013). The CPT is a method of experimentally induced pain and mimics the pain experienced within chronic conditions effectively and is considered to be safe (von Baeyer, Piira, Chambers, Trapanotto, & Zeltzer, 2005; Mitchell, MacDonald, & Brodie, 2004). The circulatory nature of this apparatus ensured that heat cannot build up around the hand, and the temperature remains a constant three degrees Celsius throughout the test (von Baeyer et al. 2005). Moreover, the apparatus had a digital thermometer to ensure the water was maintained at the same temperature for all participants, ensuring equivalence of pain stimulus.

Pain perception measures

Two measurements were recorded of pain perception during this research; objective pain tolerance and subjective pain intensity. The time period, measured in seconds, in which participants kept their hand immersed in the cold-water bath was the measurement of pain tolerance in this study. Participants were informed that, when they cannot withstand any pain they may feel, they should remove their hand (Rutchick and Slepian 2013). Thus, immersion time is the result of the time period in which participants can tolerate the pain and when participants do remove their hand from the water bath, this highlights that they can no longer tolerate the pain. Pain Intensity at the most painful moment during the CPT was measured using a digital visual analogue scale (VAS) between 0 and 100. 0 represented no pain sensation and 100 represented the most intense pain sensation imaginable (Locher et al. 2017). Participants were asked to move a digital slider to the most accurate representation of their pain intensity, with the chosen number rating being clearly indicated on the computer screen. VAS's have been found to have good validity and excellent reliability (de Boer et al. 2004).

Reading Comprehension Task (k5 Learning, 2014)

A reading comprehension task was given to participants as a filler task between the two cold pressor tests. This was included in order to minimise pain sensitisation effects for the second cold pressor task. The reading comprehension task included four reading tasks of a low level to ensure participants did not find them too challenging. Each text had its own set of questions included in the participant handbook. The titles of the four texts, in order of how they appeared in the task are as follows; 'what

are clouds?', 'Mount Rushmore; Birth, expansion, preservation, and development', 'the sun and the stars', and 'the ice age'. The majority of participants did not complete all texts as this was only a filler task.

2.4. Procedure

The School ethics committee were presented with all participant materials and procedures before granting permission to conduct this study. Participant materials included information sheets providing sufficient information for participants to give informed consent to take part in the study, consent forms and debrief sheets. Participants were aware that they could withdraw from the study at any time and that they could withdraw their data up to a provided date. Consequently, full ethical approval was granted by the University's ethics committee.

Participants were welcomed into the laboratory, with a brief introduction from the researcher. Participants were informed that the computer screen will guide them through the research process and that the researcher will intervene when needed. The first instruction given to participants on the computer screen was to read the information sheet and fill in the consent form.

The information sheet stated that the purpose of this research was to investigate individual differences within pain perception. Moreover, those in the OLP condition were informed that they will be given a placebo nasal spray and those in the DP condition were informed that they will be given a painkiller nasal spray. It also informed participants about the basic procedure, risks and benefits of taking part in this research, the regulations regarding the handling of their data and their ethical rights. Furthermore, participants were informed of any medical conditions which mean they cannot continue with the research. Exception medical conditions are as follows; acute or chronic pain, cardiovascular problems, arthritis, diabetes, fibromyalgia, Reynaud's Disease, circulatory problems (Rutchick and Slepian 2013). It was also stated that, if in the rare case that individuals are allergic to sodium chloride, they should not participate. All exception criterion was clearly stated on all recruitment materials. After the opportunity to ask questions, participants filled in the consent form which they signed, with the researcher checking and countersigning the consent form. Participants were then asked to fill in the demographic questionnaire before completing the first baseline CPT.

Participants were given a list of CPT instructions on the computer screen with the opportunity to ask any questions after reading them. Participants were instructed to roll up the sleeves on their left hand and remove any jewellery on their left wrist or left hand. Furthermore, they were informed that they should listen to the researcher's instructions when to immerse their hand to ensure an accurate time was recorded. When asked to immerse their hand, participants were instructed to place it in the cold-water bath up to their wrist, approximately where they would wear a watch. Participants were told that when they cannot withstand any pain they may feel, they should remove their hand and inform the researcher as soon as they do so. This allows for an accurate recording of pain tolerance. Moreover, participants were told that if they leave their hand in the water for the maximum time, the researcher will inform them when to withdraw their hand. It must be stated that although this was said, participants were not informed what the maximum time was until the debrief. Participants were told that they will be given the opportunity to record their pain intensity after the CPT and that it is important that they do not verbally communicate with the researcher during the CPT. After participants were given these instructions, they completed the baseline CPT. Participants who immersed their hand for three minutes were asked to remove their hand after this time period (Rutchick and Slepian 2013). When participants had removed their hand, they were asked to rate their pain intensity on a visual analogue scale between 0 (no pain sensation) and 100 (the most intense pain imaginable).

To ensure participants' hands had a sufficient time period to regain a normal temperature before completing the post-treatment CPT, a 15-minute time period was ensured between the baseline and post-treatment CPT. During this time period participants were asked to complete three personality questionnaires; BFI-2, BIS/BAS scales and LOT-R. Participants were not given the names of the questionnaires. Participants were given the original instructions for each questionnaire and were prompted to read the instructions for each questionnaire carefully. This usually took approximately 5-10 minutes meaning it was important to have another task which would fill the remainder of the 15-minute time period. Thus, the basic reading comprehension task was given once the questionnaires were completed.

Given the reading comprehension task was an unrelated filler task, participants were not required to read all the texts and those in the NT group only completed the task for the remainder of the 15-minute time period whereby the researcher asked the participants to stop the task. For those in the OLP and DP groups, they were asked to stop the reading task at approximately 12 minutes as they

were required to read the placebo information sheet or painkiller information sheet. Those in the NT group were not given any additional information sheets.

Once those in the OLP and DP groups read the additional information sheet[1], the researcher gave them a basic recap of what the information sheets stated and prepared the nasal spray for use. Participants were asked to administer the placebo following the instructions provided to them. After administering the placebo participants were instructed to wait 30 seconds before they completed the post-treatment CPT and were advised that they should stay silent within this time period. Those in the NT group were not given any treatment.

Participants then completed the post-treatment CPT following the same instructions as the baseline CPT. Following this, participants were informed that the practical part of the study was complete and they were asked to complete the FPQ-III.

Participants were, finally, directed to read the debrief sheet in the final page of their booklet. Firstly, in the debrief sheet, participants were thanked for participating in the study. Given the true aims of the study were withheld from participants within the information sheet, it was important to reveal the study's true aims. Those in the NT and OLP groups were told the true aim of this research was to investigate the OLP in terms of whether personality-related variables predict OLP responding. As recruitment for the DP group occurred at a later date, those in the OLP and NT groups were not informed about the additional DP group. However, in participant's consent forms they agreed to their data being used externally to the research they participated in. Those in the DP group were informed that they received a placebo and that the effectiveness of the DP will be compared to the OLP and NT groups, and that the influence of personality within DP and OLP responding will be compared. The debrief sheet also re-stated the data protection regulations mentioned in the information sheet to ensure participants understood the correct way in which their data will be handled. In addition to this, instructions were given informing participants how to withdraw their data and the date which they will need to withdraw it by if they wish to do so. Contact details were also provided to give participants the opportunity to withdraw their data and ask any further questions.

[1] See 'information provided to the OLP condition' and 'information provided to the DP condition' sub-sections within section 2.3.

2.5. Data analysis

Firstly, demographic information was analysed to ensure there were no demographic differences between treatment groups. Regarding age, a one-way ANOVA was conducted with treatment group as the independent variable and age as a continuous dependent variable. Maintaining treatment group as the independent variable, chi-squared analyses were conducted with sex, marital status and painkiller usage to ensure experimental conditions did not significantly differ on these factors.

To analyse hypothesis one, two separate one-way ANCOVAs were conducted; with one analysis conducted for objective pain tolerance and one for subjective pain intensity. Treatment group (OLP, DP and NT) was entered as the independent variable, with the post-treatment measurement of pain tolerance or intensity entered as the dependent variable. The corresponding baseline measurement of pain perception was inputted as a covariate to ensure any individual differences between groups were controlled for within the analyses. If there were statistically significant differences between treatment groups, planned contrasts were conducted to highlight between which groups any differences exist.

To perform exploratory analysis to highlight whether personality-related variables predicted placebo responding, several hierarchical multiple regressions were conducted. Each regression analysis contained three steps, using the 'forced entry' method. The dependent variable for each multiple regression was post-treatment pain tolerance or post-treatment pain intensity. Within the first step, the corresponding baseline measurement of pain perception (either tolerance or intensity) was entered as a covariate (Model 1). Within the second step, the mean centred score for the personality variable of interest was entered, along with the dummy codes for the NT group and the DP group (Model 2). To further explain this, the NT dummy code meant that all participants in the NT were coded as 1 with participants in the OLP and DP coded as 0. For the DP dummy code, all participants in the DP group were coded as 1 with participants in the OLP and NT groups coded as 0. Thus, participants in the OLP were always coded as 0 within this analysis. Furthermore, the mean centred score for each personality-related variable was used as an alternative to the raw mean scores as it is argued to reduce the level of multicollinearity (Shieh 2011). Within the third and final step, the interactions between the personality trait of interest and the NT group and DP group were entered, with the OLP group as the reference group (Model 3). By selecting the OLP group as the reference group, this meant analysis could highlight whether there were any personality-related variables which moderated placebo

effectiveness between the OLP and NT groups and the OLP and DP groups. Thus, two interactions were investigated for each personality-related variable; NT X personality-related variable and DP X personality-related variable, both in comparison to the OLP group. In the event that significant interactions were found, simple slopes were created using ModGraph 3.0 to further understand the interaction (Jose, 2013).

3. Results

3.1. Sample Characteristics

The three treatment groups did not differ on age ($F_{(2, 73)} = .36$, $p = .701$), sex ($X^2_{(2)} = 4.50$, $p = .105$), marital status ($X^2_{(6)} = 5.71$, $p = .457$), or painkiller usage within 4 hours prior to participating in the study ($X^2_{(2)} = 4.11$, $p = .128$).

3.2. Objective pain tolerance and placebo analgesia

Descriptive statistics for Hypothesis One are displayed in Table 1. Furthermore, Figure 1 demonstrates the mean pain tolerance for the baseline and post-treatment CPT for each treatment group, with higher pain tolerance scores representing the ability to experience pain for a longer period of time.[2]

Table 1. Table showing the means and standard deviations for Hypothesis 1.

		Pain Tolerance (seconds)			Pain Intensity		
		N	Mean	SD	N	Mean	SD
Baseline CPT	NT	24	46.50	27.15	24	59.79	17.66
	OLP	25	48.36	26.20	25	61.60	20.67
	DP	26	39.50	22.05	26	48.23	19.88
Post-treatment CPT	NT	24	46.04	36.71	24	67.58	16.93
	OLP	25	58.76	46.65	25	61.72	20.01
	DP	26	46.85	33.94	26	48.15	22.98

A one-way ANCOVA was carried out to investigate whether there were any statistically significant differences between treatment groups within post-treatment pain tolerance when controlling for baseline pain tolerance. Several assumptions were met including homogeneity of regression slopes, homogeneity of variance ($p > .05$), and the covariate was linearly related to the dependent variable within each treatment group; demonstrated by visual inspection and positive, significant correlations between the covariate and dependent variable for each treatment group. However, normality and homoscedasticity assumptions were violated. Normality assumptions, in this case, can be waived due to central limit theorem (Field, 2009). On the contrary, the violation of homoscedasticity was addressed using a log transformation; leading to no longer violating the assumption of

[2] Descriptive statistics surrounding pain tolerance are included in more detail within Appendix 4.

homoscedasticity and the data being normally distributed (Leard statistics, 2017). Furthermore, significant outliers were identified, however, they were not excluded from the data. The transformed data were plotted to complete a visual inspection to ensure there were no clear and obvious extreme values which did not follow the general data trend. Furthermore, the analysis was conducted with and without the outliers to confirm that the presence of the outliers did not change the results with regards to what is and is not significant. Therefore, this suggests that it is acceptable to keep those significant outliers, with caution (Laerd Statistics, 2017).

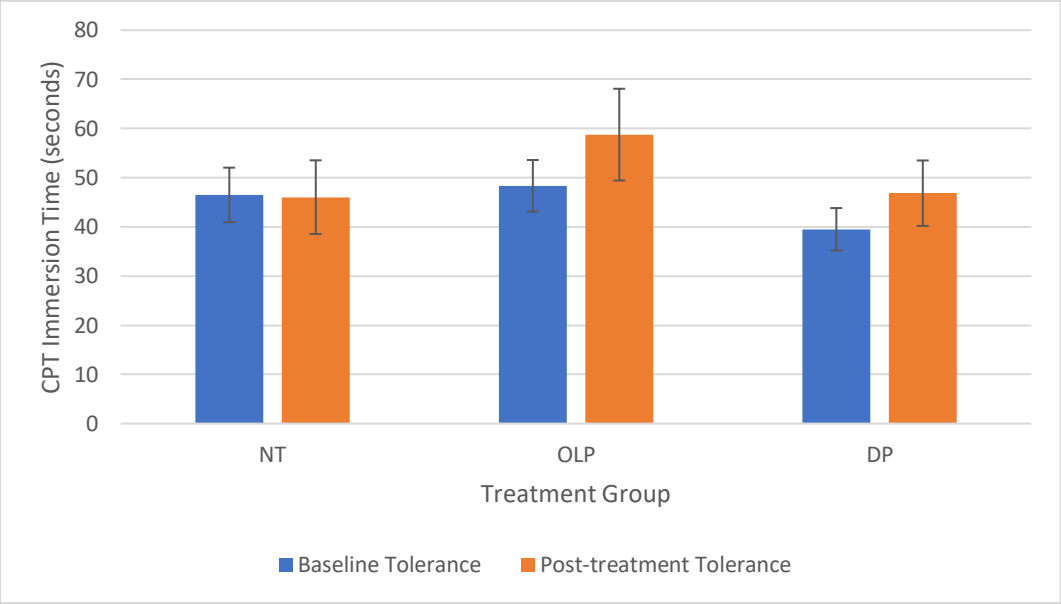

Figure 1. Bar chart showing the mean CPT times for treatment groups within the baseline and post-treatment CPT. Error bars are SEM.

The one-way ANCOVA revealed no statistically significant differences between the treatment groups, $F(2, 71) = 1.90$, $p = .157$, $\eta^2 = .051$, observed power = .38. This demonstrates that there were no significant differences between the experimental groups, suggesting that placebo analgesia did not occur with objective pain tolerance. Furthermore, the covariate was significant, $F(1, 71) = 196.26$, $p < .001$, $\eta^2 = .73$, which highlights the importance of controlling for baseline pain tolerance and, thus, controlling for individual differences in baseline pain tolerance within this analysis.[3]

[3] When including participants who were excluded due to the ceiling effect of baseline CPT times, the results were different. There were significant differences between groups, with contrasts revealing significant differences between the OLP and NT groups ($p < .05$) and the DP and NT groups ($p < .05$). There were no significant differences between the OLP and DP groups.

3.3. Subjective pain intensity and placebo analgesia

Means and standard deviations for pain intensity are stated in Table 1. As shown in Figure 2, the mean pain intensity score for the NT group increases in the post-treatment CPT. However, when referring to the OLP and DP treatment groups, there is little change in the average pain intensity before and after receiving a placebo.

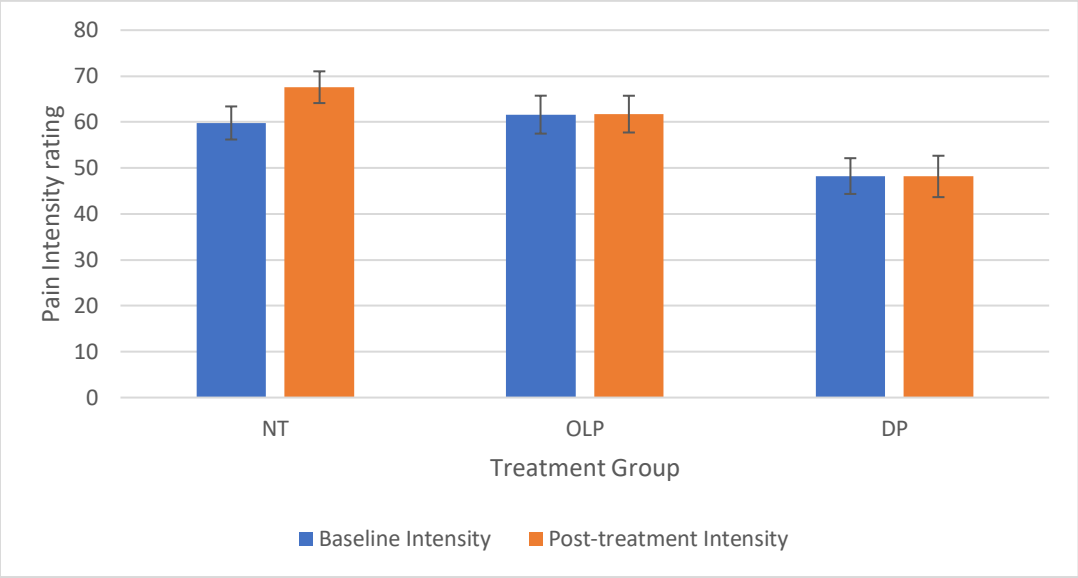

Figure 2. Bar chart showing the mean pain intensity scores for treatment groups within the baseline and post-treatment CPT. Error bars are SEM.

A one-way ANCOVA was carried out to test if there were any significant differences between groups within post-treatment pain intensity, whilst controlling for baseline pain intensity. Assumptions met included the covariate and dependent variable being linearly related, and there was homogeneity of regression slopes and homogeneity of variance. In addition, the assumption of a normal distribution was met, demonstrated by the Shapiro Wilk test with $p > .05$, and there was homoscedasticity, as demonstrated by visual inspection. There was one significant outlier, however, this was not removed as it did not significantly influence data analysis and close inspection revealed that the intensity ratings were reasonable and in line with the general data trend.[4] The ANCOVA revealed a statistically significant difference for treatment group, $F(2, 71) = 4.84$, $p = .011$, $\eta^2 = .12$, observed power = .78.

[4] The individual's baseline pain intensity rating was 22, increasing to 29 in the post-treatment intensity rating. This was in line with the general trend with participants in the NT group experiencing an increase in pain intensity within the post-treatment CPT.

The covariate was also significant, $F(1, 71) = 173.41$, $p < .001$, $\eta^2 = .71$, highlighting the importance of controlling for baseline pain intensity.

Planned contrasts revealed that there were significant differences within post-treatment pain intensity when comparing the OLP and the NT groups ($p = .020$, 95% CI [-13.69, -1.19]) and the DP and the NT groups ($p = .005$, 95% CI [-15.70, -2.95]). This demonstrates that receiving a placebo, regardless of whether participants believed it was a placebo or a painkiller, enabled them to feel significantly less pain in the post-treatment CPT compared to those who did not receive a placebo. Planned contrasts between the OLP and DP groups revealed no statistically significant differences ($p = .558$, 95% CI [-4.49, 8.26]). This suggests that open-label placebos and deceptive placebos are equally effective when ensuring participants do not experience an increase in pain intensity within the second CPT.[5]

[5] When conducting analysis with participants who were excluded due to the ceiling effect, there was a significant difference between all groups, with significant differences between the OLP and NT groups ($p < .05$) and DP and NT groups ($P < .01$). There were no significant differences between the OLP and DP groups.

3.4. Association between personality-related variables and objective pain tolerance, comparing the NT and DP groups to the OLP group.

To briefly summarise the method in which exploratory analyses were conducted, separate regression analyses were conducted for each personality trait with three steps. The post-treatment outcome (either post-treatment tolerance or post-treatment intensity) was entered as the dependent variable, with the first step including the corresponding outcome at baseline (either baseline tolerance or baseline intensity) as a covariate. The second step within each regression included the personality trait and dummy coded variables for the NT and DP groups (with the OLP group as the reference group). The final model included the personality trait X NT group and personality trait X DP group interactions, both in comparison to the OLP group. The key variables of interest are the two interactions as they demonstrate whether personality traits may predict OLP responding and whether personality may influence OLP and DP responding in differing ways.

Optimism. The final step revealed the model as a whole was significant, $F(6, 73) = 17.55$, $p < .001$, explaining a total of 61% of the variance of pain tolerance. Baseline pain tolerance was the only significant predictor variable ($\beta = .75$, $p < .001$).

Open-Mindedness. The final step revealed the model as a whole was significant, $F(6, 74) = 17.12$, $p < .001$, explaining a total of 60% of the variance of pain tolerance. Baseline pain tolerance was the only significant predictor variable ($\beta = .75$, $p < .001$).

Conscientiousness The final step revealed the model as a whole was significant, $F(6, 73) = 16.43$, $p < .001$, explaining a total of 60% of the variance of pain tolerance. Baseline pain tolerance was the only significant predictor variable ($\beta = .75$, $p < .001$).

Extraversion. The final step revealed the model as a whole was significant, $F(6, 72) = 22.21$, $p < .001$, explaining a total of 67% of the variance of pain tolerance. Baseline pain tolerance was the only significant predictor variable ($\beta = .83$, $p < .001$), although extraversion was marginally significant ($\beta = -.24$, $p = .051$).

Agreeableness. The final step revealed the model as a whole was significant, $F(6, 72) = 17.13$, $p < .001$, explaining a total of 61% of the variance of pain tolerance. Baseline pain tolerance was the only significant predictor variable ($\beta = .75$, $p < .001$).

Negative Emotionality. The final step revealed the model as a whole was significant, $F(6, 72) = 18.93$, $p < .001$, explaining a total of 63% of the variance of pain tolerance. Baseline pain tolerance was the only significant predictor variable ($\beta = .78$, $p < .001$).

BIS. The final step revealed the model as a whole was significant, $F(6, 73) = 18.27$, $P < .001$, explaining a total of 62% of the variance of pain tolerance. Baseline pain tolerance was the only significant predictor variable ($\beta = .76$, $p < .001$).

BAS Drive. The final step revealed the model as a whole was significant, $F(6, 72) = 18.63$, $p <.001$, explaining a total of 63% of the variance of pain tolerance. Baseline pain tolerance was the only significant predictor variable ($\beta = .76$, $p < .001$).

BAS Reward Responsiveness. The final step revealed the model as a whole was significant, $F(6, 72) = 15.75$, $p < .001$, explaining a total of 59% of the variance of pain tolerance. Baseline pain tolerance was the only significant predictor variable ($\beta = .73$, $p < .001$).

BAS Fun seeking. The final step revealed the model as a whole was significant, $F(6, 73) = 17.59$, $p < .001$, explaining a total of 61% of the variance of pain tolerance. Baseline pain tolerance was the only significant predictor variable ($\beta = .77$, $p < .001$).

Fear of Pain. The final step revealed the model as a whole was significant, $F(6, 67) = 20.25$, $p < .001$, explaining a total of 67% of the variance of pain tolerance. Significant predictors of post-treatment pain tolerance were baseline pain tolerance ($\beta = .77$, $p < .001$) and fear of pain $\beta = .39$, $p = .002$).

Fear of Severe Pain. The final step revealed the model as a whole was significant, $F(6, 71) = 17.47$, $p < .001$, explaining a total of 62% of the variance of pain tolerance. Baseline pain tolerance ($\beta = .77$, $p < .001$) and the NT dummy code ($\beta = -.19$, $p = .044$) were significant predictors of fear of severe pain.

Fear of Medical Pain. The final step revealed the model as a whole was significant, $F(6, 74) = 18.99$, $p < .001$, explaining a total of 63% of the variance of pain tolerance. Baseline pain tolerance ($\beta = .79$, $p < .001$) and fear of medical pain ($\beta = .28$, $p = .045$) were significant predictors of post-treatment pain tolerance.

Fear of Minor Pain. The final step revealed the model as a whole was significant, $F(6, 70) = 22.22$, $p < .001$, explaining a total of 68% of the variance of pain tolerance. Significant predictors of post-treatment pain tolerance were baseline pain tolerance ($\beta = .76$, $p < .001$), fear of minor pain ($\beta = .38$, $p = .001$) and the fear of minor pain X DP interaction (with reference to the OLP group; $\beta = -.21$, $p = .032$). *See Table 2.*

To further investigate the interaction highlighted in this regression, simple slopes were plotted for the relationship between experimental condition and post-treatment pain tolerance for high levels of fear of minor pain (1SD above the mean), medium levels (the mean) and low levels of fear of minor pain (1SD below the mean) using ModGraph 3.0 (Jose, 2013). Simple slopes revealed that fear of minor pain is positively associated with post-treatment pain tolerance within the OLP group, however, fear of minor pain does not appear to moderate the effectiveness of DP responding. Therefore, it can be suggested that those who score higher on fear of minor pain experience an enhanced level of placebo analgesia within the OLP group. *See Figure 3*.

Table 2. Table showing summary of multiple regression, with post-treatment pain tolerance as the dependent variable whereby the fear of minor pain X DP interaction is significant, with reference to the OLP group.

	R	R^2	R^2 change	B	SE	β	t
Model 1	.76	.57***					
Baseline pain tolerance				1.20	0.13	.76***	9.59
Model 2	.81	.65**	.08**				
Baseline pain tolerance				1.24	.12	.78***	10.53
Fear of minor pain (FOminP)				1.61	.47	.26**	3.41
NT dummy code				-7.17	7.29	-.08	-.99
DP dummy code				-1.38	7.18	-.02	-.19
Model 3	.82	.68	.03				
Baseline pain tolerance				1.20	.12	.76***	10.28
FOminP				2.38	.66	.38**	3.62
NT dummy code				-5.68	7.29	-.07	-.78
DP dummy code				.57	7.06	.01	.08
FOminP X NT interaction *(OLP group as reference)*				-.13	1.28	-.01	-.10
FOminP X DP interaction (OLP group as reference)				-2.30	1.05	-.21*	-2.19

Note: * p < .05, ** p < .01, *** p < .001

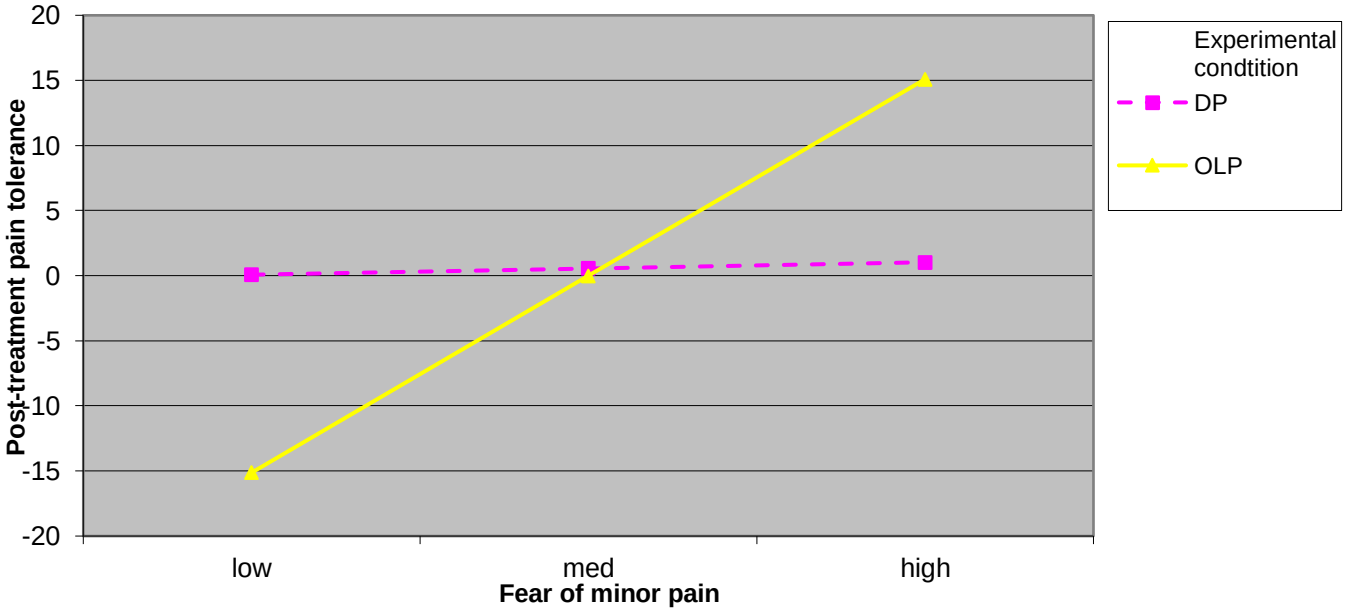

Figure 3. Graph showing simple slopes for the relationship between experimental condition and post-treatment pain tolerance, moderated by fear of minor pain.

3.5. Association between personality-related variables and subjective pain intensity, comparing the NT and DP groups to the OLP group.

Optimism. The final step revealed the model as a whole was significant, $F(6, 73) = 36.65$, $p < .001$, explaining a total of 77% of the variance of pain intensity. The only significant predictors within the overall model were the NT dummy code ($\beta = .16$, $p = .022$) and baseline pain intensity ($\beta = .80$, $p < .001$).

Open-Mindedness. The final step revealed the model as a whole was significant, $F(6, 74) = 32.26$, $p < .001$, explaining a total of 76% of the variance of pain intensity. The only significant predictors of post-treatment pain intensity were the NT dummy code ($\beta = .15$, $p = .031$) and baseline pain intensity ($\beta = .82$, $p < .001$).

Conscientiousness. The final step revealed the model as a whole was significant, $F(6, 73) = 36.48$, $p < .001$, explaining a total of 77% of the variance of pain intensity. Baseline pain intensity was the only significant predictor within the overall model ($\beta = .81$, $p < .001$).

Extraversion. The final step revealed the model as a whole was significant, $F(6, 72) = 31.56$, $p < .001$, explaining a total of 74% of the variance of pain intensity. The only significant predictors of post-treatment pain intensity were baseline pain intensity ($\beta = .79$, $p < .001$) and the NT dummy code ($\beta = .18$, $p = .020$).

Agreeableness. The final step revealed the model as a whole was significant, $F(6, 72) = 39.91$, $p < .001$, explaining a total of 78% of the variance of pain intensity. There were several significant predictors of post-treatment pain intensity; baseline pain intensity ($\beta = .82$, $p < .001$), agreeableness X DP interaction (with the OLP group as the reference; $\beta = .25$, $p = .007$), the NT dummy code ($\beta = .18$, $p = .008$) and agreeableness ($\beta = -.24$, $p = .031$). *See Table 3*.

Given there was a significant interaction identified in this analysis, additional analysis was conducted. Simple slopes were plotted for the relationship between experimental condition (OLP and DP) and post-treatment pain intensity for high levels of agreeableness (1SD above the mean), medium levels

(the mean) and low levels of agreeableness (1SD below the mean) using ModGraph 3.0 (Jose, 2013). Simple slopes revealed post-treatment pain intensity was positively associated with agreeableness within the DP group, thus, given lower intensity scores represent placebo analgesia, those who scored lower on agreeableness were more likely to experience placebo analgesia. However, there was a negative association between post-treatment pain intensity and agreeableness for those in the OLP group, suggesting those who score higher on agreeableness are more likely to respond to open-label placebos when reducing pain intensity. *See Figure 4*.

Table 3. Table showing summary of multiple regression, with post-treatment pain intensity as the dependent variable whereby the agreeableness X DP interaction is significant, with reference to the OLP group.

	R	R^2	R^2 change	B	SE	β	t
Model 1	.85	.72***					
Baseline pain intensity				.91	.07	.85***	13.44
Model 2	.87	.76*	.04*				
Baseline pain intensity				.87	.07	.82***	13.08
Agreeableness				-.10	.21	-.03	-.45
NT dummy code				8.32	3.21	.18*	2.60
DP dummy code				-1.89	3.20	-.04	-.59
Model 3	.89	.78*	.03*				
Baseline pain intensity				.88	.07	.82***	13.60
Agreeableness				-.88	.40	-.24*	-2.21
NT dummy code				8.44	3.08	.18**	2.74
DP dummy code				-1.82	3.07	-.04	-.59
Agreeableness X NT interaction *(OLP group as reference)*				.65	.54	.11	1.22
Agreeableness X DP interaction (OLP group as reference)				1.42	.52	.25**	2.76

Note: * p < .05, ** p < .01, *** p < .001

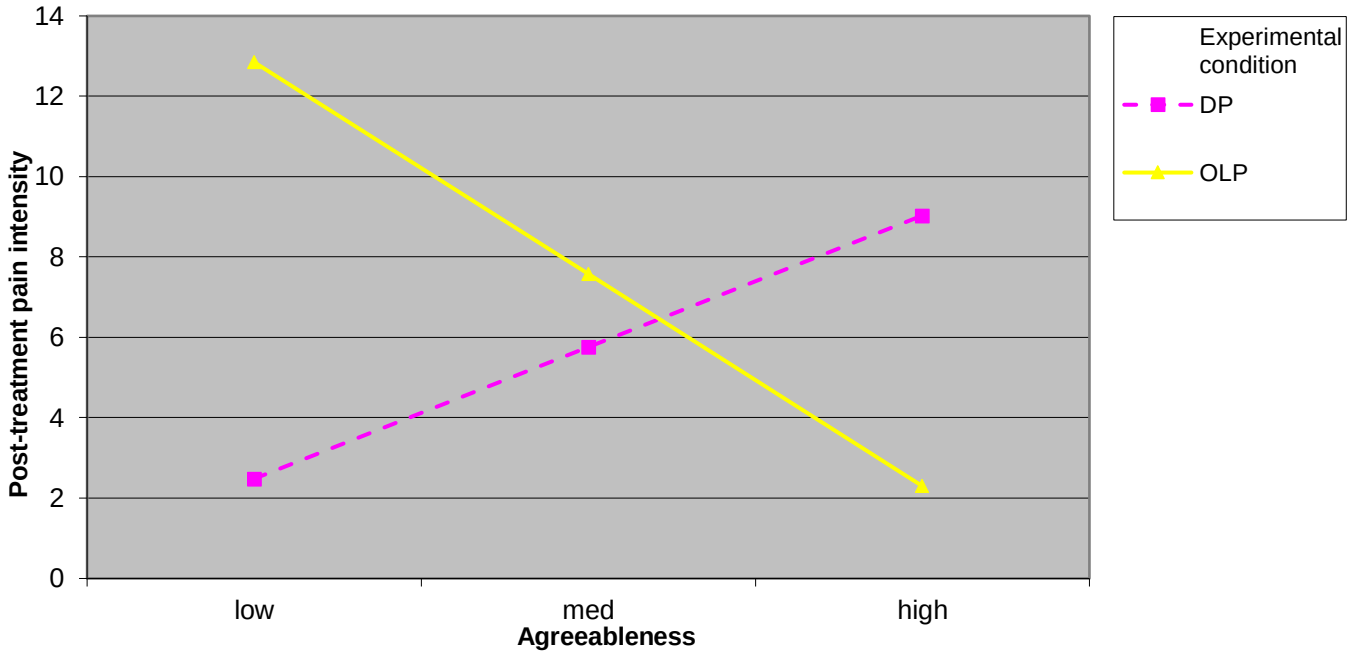

Figure 4. Graph showing the simple slopes for the relationship between experimental condition and post-treatment pain intensity, moderated by agreeableness.

Negative Emotionality. The final step revealed the model as a whole was significant, $F(6, 72) = 36.04$, $p < .001$, explaining a total of 77% of the variance of pain intensity. The significant predictors within the overall model were baseline pain intensity ($\beta = .82$, $p < .001$) and the NT dummy coded variable ($\beta = .15$, $p = .035$).

BIS. The final step revealed the model as a whole was significant, $F(6, 73) = 33.86$, $p < .001$, explaining a total of 75% of the variance of pain intensity. The only significant predictor of post-treatment pain intensity within the overall model was baseline pain intensity ($\beta = .81$, $p < .001$).

BAS Drive. The final step revealed the model as a whole was significant, $F(6, 72) = 32.85$, $p < .001$, explaining a total of 75% of the variance of pain intensity. The significant predictors within the overall model were baseline pain intensity ($\beta = .82$, $p < .001$) and the NT dummy code ($\beta = .16$, $p = .030$).

BAS Reward Responsiveness. The final step revealed the model as a whole was significant, F(6, 72) = 35.90, p < .001, explaining a total of 77% of the variance of pain intensity. Within the overall model the significant predictors were baseline pain intensity (β = .82, p < .001) and the NT dummy code (β =.14, p = .046).

BAS Fun Seeking. The final step revealed the model as a whole was significant, F(6, 73) = 35.43, p < .001, explaining a total of 76% of the variance of pain intensity. The significant predictors within the overall model were baseline pain intensity (β = 81, p < .001) and the NT dummy code (β = .15, p = .038).

Fear of Pain. The final step revealed the model as a whole was significant, F(6, 67) = 32.39, P < .001, explaining a total of 76% of the variance of pain intensity. The only significant predictors within the overall model were baseline pain intensity (β = .81, p < .001) and the NT dummy code (β =.17, p = .023).

Fear of Severe Pain. The final step revealed the model as a whole was significant, F(6, 71) = 33.09, p < .001, explaining a total of 75% of the variance of pain intensity. The only significant predictors within the overall model were baseline pain intensity (β = .83, p < .001) and the NT dummy code (β =.18, p = .018).

Fear of Minor Pain. The final step revealed the model as a whole was significant, F(6, 70) = 37.90, P < .001, explaining a total of 78% of the variance of pain intensity. The only significant predictor within the overall model was baseline pain intensity (β =.84, p < .001).

Fear of Medical Pain. The final step revealed the model as a whole was significant, F(6, 74) = 37.59, p < .001, explaining a total of 77% of the variance of pain intensity. Significant predictors included baseline pain intensity (β = .81, p < .001), NT dummy coded variable (β = .15, p = .028), and fear of medical pain X DP interaction, with the OLP group as the reference, was also significant (β = -.19, p = .039). *See Table 4.*

Given there was a significant interaction within the overall model, additional analysis was conducted to understand the interaction further. Simple slopes were plotted for the relationship between experimental condition (OLP and DP) and post-treatment pain intensity for high levels of fear of medical pain (1SD above the mean), medium levels (the mean) and low levels of fear of medical pain (1SD below the mean) using ModGraph 3.0 (Jose, 2013). Simple slopes revealed that there was a positive association between post-treatment pain intensity and fear of medical pain for those in the OLP group, with lower levels of fear of medical pain predicting placebo analgesia. However, there was a negative association between post-treatment pain intensity and fear of medical pain for those in the DP group, with higher levels of fear of medical pain predicting placebo analgesia. *See Figure 5.*

Table 4. Table showing summary of multiple regression, with post-treatment pain intensity as the dependent variable whereby the interaction between fear of medical pain X DP is significant, with reference to the OLP group.

	R	R^2	R^2 change	B	SE	β	t
Model 1	.85	.72***					
Baseline pain intensity				.91	.07	.85***	13.63
Model 2	.87	.75*	.04*				
Baseline pain intensity				.88	.07	.82***	12.96
Fear of medical pain (FOmedP)				-.09	.15	-.04	-.58
NT dummy code				7.57	3.16	.17*	2.40
DP dummy code				-1.59	3.25	-.04	-.49
Model 3	.88	.77	.02				
Baseline pain intensity				.86	.07	.81***	12.54
FOmedP				.38	.28	.15	1.37
NT dummy code				7.01	3.12	.15*	2.26
DP dummy code				-2.07	3.20	-.05	-.65
FOmedP X NT interaction *(OLP group as reference)*				-.51	.37	-.12	-1.37
FOmedP X DP interaction (OLP group as reference)				-.79	.37	-.19*	-2.10

Note: * p < .05, ** p < .01, *** p < .001

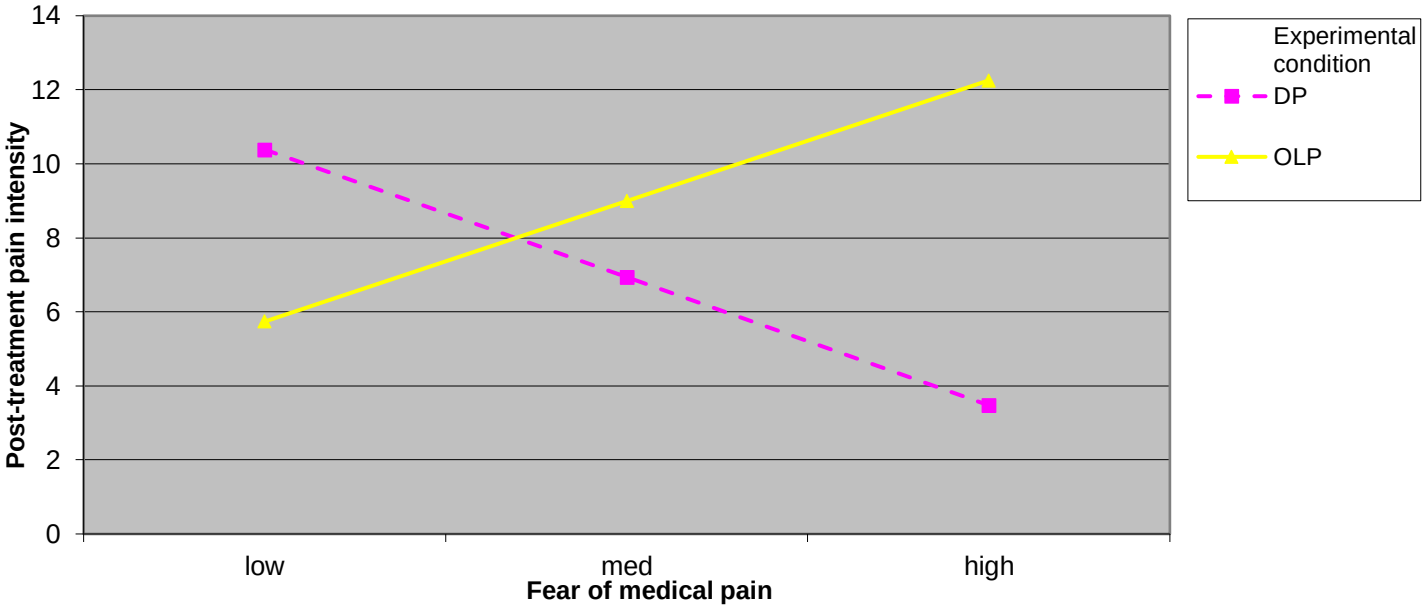

Figure 5. Graph showing the simple slopes for the relationship between experimental condition and post-treatment pain intensity, moderated by fear of medical pain.

4. Discussion

This study addressed the lack of research comparing OLP and DP effectiveness, and whether personality-related variables influence OLP responding. Analysis of the role of OLPs and DPs on pain intensity revealed that the two placebo groups experienced significantly less pain intensity after receiving a placebo, compared to those who received no treatment. Furthermore, there were no significant differences between the OLP and DP groups within pain intensity ratings, demonstrating placebos with and without deception to be equally as effective within this study. Within pain tolerance times, however, there were no differences between groups after receiving a placebo. In other words, placebo analgesia was only observed in subjective pain intensity ratings, with neither OLPs or DPs increasing objective pain tolerance. Finally, in our exploratory analyses of personality variables, we found that agreeableness, fear of minor pain and fear of medical pain moderated the effectiveness of OLP analgesia relative to DP analgesia.

4.1. Summary of exploratory findings

Exploratory analysis investigated whether personality-related variables predicted the effectiveness of OLP analgesia, compared to those in the DP and NT groups. Firstly, analysis of objective pain tolerance revealed that higher levels of fear of minor pain may predict placebo analgesia within the OLP group, but not in the DP group. For subjective pain intensity, it can be suggested that agreeableness and fear of medical pain may also influence placebo analgesia for the OLP and the DP groups. There was a positive association between agreeableness and pain intensity within the DP group, suggesting that those who scored lower on agreeableness were more likely to experience subjective pain relief. However, there was a negative association between agreeableness and pain intensity within the OLP group, with higher agreeableness scores suggesting enhanced placebo analgesia. Finally, fear of medical pain may also moderate the effectiveness of an OLP and DP for placebo analgesia within subjective pain intensity. There was a positive association between pain intensity and fear of medical pain within the OLP group, with lower fear of medical pain scores suggesting enhanced placebo analgesia. In contrast, there was a negative association between pain intensity and fear of medical pain within the DP group, with higher scores suggesting increased placebo effectiveness.

Analysis revealed that the following personality-related variables did not predict placebo analgesia for objective pain tolerance or subjective pain intensity; extraversion, open-mindedness, negative emotionality, conscientiousness, optimism, BIS, BAS drive, BAS reward responsiveness, BAS fun-seeking, fear of pain (overall score), and fear of severe pain.

4.2. Open-label placebos

Open-label placebos have been found to be effective in many cases with various medical conditions (Carvalho et al. 2016; Hoenemeyer et al. 2018; Kam-Hansen et al. 2014; Kaptchuk et al. 2010; Kelley et al. 2012; Sandler and Bodfish 2008; Schaefer et al. 2016, 2018; Zhou et al. 2019) and with healthy participants (El Brihi et al. 2019; Locher et al. 2017; Meeuwis et al. 2018). However, there is only a small amount of literature comparing an OLP with a DP (Barnes et al. 2019; Locher et al. 2017). This current study replicated the findings of Locher et al. (2017), finding that a DP and OLP with a rationale are equally as effective when decreasing pain intensity. This suggests that deception may not be necessary within placebo analgesia, as this study and Locher et al. (2017) have found placebos given openly are equally as effective as placebos given deceptively when reducing subjective outcomes. Furthermore, Locher et al. (2019) and Mathur et al. (2018) highlighted no OLP effects with objective measures which is also consistent within this research, finding no placebo effects with objective pain tolerance. This suggests OLP effects may be limited to subjective outcomes, also a consistent finding within DP literature, with deceptive placebos often only influencing subjective outcomes (Breidert and Hofbauer 2009; Hróbjartsson and Gøtzsche 2001; Kaptchuk and Miller 2015).

4.3. Expectancy and conditioning theories

With expectancy and conditioning being identified as the key theories explaining the placebo effect (Stewart-Williams and Podd 2004), it is possible to suggest that expectancy more suitably provides an explanation for the OLP and DP analgesia highlighted in this research. It is possible that participants' expectations of pain relief were raised in the OLP and DP group by a rationale being provided before administering the placebo. Participants in the OLP group were informed that although they were administering a placebo, they may still experience pain relief based on previous research. Participants were also informed that having a positive attitude may increase its effectiveness. This rationale, therefore, attempted to raise the expectation of pain relief, even when participants understood the placebo was inactive. The DP group were also given a rationale to increase expectation of pain relief, informing them that they were being given a painkiller which contained Lidocaine which has been

proven to be effective in studies worldwide. This suggests that given those in the OLP and DP groups were provided with statements to increase expectation of pain relief after receiving a placebo, this may have led to participants having an expectation of pain relief, consequently leading to the reduction in pain experienced by those in the OLP and DP groups, compared to the NT group. Furthermore, Locher et al. (2017) found an OLP without a rationale, was not as effective as a placebo with a rationale. Given expectancy was not measured in this research, it would be useful to include a measurement of expectancy in any replication of this study. Conditioning, however, is a very unlikely theory to explain the findings in this study. For individuals to have a conditioned response of placebo analgesia obtained through the use of a nasal painkiller, it would rely on participants having repeatedly used a nasal painkiller. Thus, it is unlikely that all participants who experienced a placebo effect had used a nasal painkiller.

4.4. Open-label placebo analgesia and personality

Various studies have suggested personality traits predict DP responding (Darragh et al. 2014; Geers et al. 2010; Lyby et al. 2010; Peciña et al. 2013; Vachon-Presseau et al. 2018), however, only one study to date has researched the influence of personality on OLP responding (Locher et al. 2019). It was found that optimism, openness to experience, locus of control, and positive attitudes towards alternative and complementary medicine did not influence OLP responding (Locher et al. 2019). Although this was the case, many other personality-related variables which have been associated with DP responding were not investigated by Locher et al. (2019). Therefore, in this study, exploratory analyses was conducted with several personality-related variables to investigate whether personality predicts OLP responding, compared to DP responding and a control group. In this study, agreeableness, fear of minor pain, and fear of medical pain were the only personality-related variables to influence OLP responding, interestingly, all in a differing way to DP responding. Given these three personality-related variables have never been measured in OLP research to our knowledge, this current study is both the first study to measure these variables and find that they appear to influence OLP responding.

4.4.1. Agreeableness

With lower pain intensity representing greater levels of placebo analgesia, an OLP was more likely to be effective if a participant scored higher on agreeableness, however, those who received a DP were more likely to experience pain relief if they scored lower on agreeableness.

Previously, agreeableness has been suggested to be a positive predictor within placebo analgesia (Peciña et al. 2013), explaining 14% of variance in the percentage change in placebo responsiveness. Although this study has also found a relationship between DP analgesia and agreeableness, it appears to be in a contradictory direction to Peciña et al. (2013) as it was found that agreeableness was negatively associated with placebo analgesia within this study. This suggests that agreeableness is likely to play some role within placebo analgesia, however, future research should attempt to understand this inconsistency.

When seeking an explanation for why increased agreeableness scores predict greater levels of OLP analgesia for subjective pain intensity, it has been suggested that those who score higher on agreeableness are more trusting (Maltby et al., 2010). This could suggest that those who are more trusting are more likely to experience placebo analgesia from an OLP. As participants knew they administered an inactive placebo, they may have been more trusting that it will be effective, particularly because of the expectation of pain relief raised before administering it. On the other hand, those who scored lower on agreeableness may be more unlikely to experience OLP analgesia as those who score lower are more likely to be suspicious and sceptical (Maltby et al., 2010). Thus, those who are suspicious and sceptical may be less likely to experience pain relief from an OLP. Furthermore, it has also been suggested that those who score higher on agreeableness are more likely to respond to treatment (Quilty et al. 2008). A further possible explanation for why those who scored higher on agreeableness are more likely to experience pain relief after receiving an OLP may be because of an interaction between dispositional and situational factors (Jakšić et al. 2013). For example, Kelley et al. (2009) found that participants who scored higher on agreeableness responded more effectively to a placebo with a warm and empathetic practitioner. This suggests that the characteristics of the researcher within this study may have interacted with agreeableness to increase the likelihood of the OLP group responding to the placebo. This, however, is speculative and would require further investigation. The relationship between agreeableness and DP responding was in the opposing direction to the OLP group, contradicting previous research (Kelley et al. 2009; Peciña et al. 2013). For this reason, it appears challenging to propose a reason for this finding. However, it is important to consider that this finding may only be present in this sample. Therefore, it is suggested that this study is replicated to ensure the findings highlighted are also replicated and these results are generalisable.

4.4.2. Fear of medical pain

Fear of medical pain was also highlighted to be an important personality-related variable predicting OLP and DP responding in opposing ways. Those who received an OLP were more likely to experience placebo analgesia if they scored lower on fear of medical pain, however, those who received a DP were more likely to experience placebo analgesia if they scored higher on fear of medical pain, with lower subjective pain intensity scores representing a greater level of placebo analgesia. Previous research investigating the role of fear of pain and placebo analgesia highlighted that fear of pain was negatively associated with placebo analgesia, with higher scoring individuals more unlikely to respond to a placebo (Lyby et al., 2012, 2010, 2011). Within this current study, the relationship between placebo analgesia and fear of medical pain within the OLP group was consistent with the findings of Lyby et al. (2010). However, for those in the DP group, this finding is inconsistent, with greater levels of fear predicting an increased likelihood of experiencing placebo analgesia.

It has previously been found that there is a positive relationship between fear of medical pain and stress, suggesting those who fear medical pain more are more likely to feel stress (Lyby et al. 2010). This suggests, measuring stress within future studies of this nature could be useful to understand this. On the other hand, when proposing an explanation for the inverse relationship between fear of medical pain and placebo analgesia within the DP group, it appears challenging given it is contradictory to previous research and theories. It may, however, be the case that those in the DP group were less stressed, with recruitment for the DP group taking place at a different time, as all participants were students and different time periods may be more stressful; for example, when completing course work for deadlines.

Given that the relationship between DP responding and agreeableness was also contradictory to previous findings, this could suggest that the results found with the DP group may not be generalisable to the general healthy population. On the other hand, if this is sample is representative of the general population, the differing direction in which agreeableness and fear of medical pain predicts OLP and DP responding could prove to be a very useful tool to use when matching individuals to treatments. Despite these findings, however, future effort should be focussed on confirming whether these findings are consistent, and if so, finding

explanations for the inverse relationship between fear of medical pain and OLP and DP responding.

4.4.3. Fear of minor pain

Finally, with regards to fear of minor pain, OLP analgesia was positively associated with fear of minor pain, however, fear of minor pain appeared to have no influence on DP responding. For the DP group, this finding is consistent with previous literature, with fear of minor pain failing to predict placebo analgesia (Lyby et al. 2010). On the other hand, OLP analgesia was predicted by fear of minor pain, suggesting it may influence OLP responding but not DP responding; thus, the role of personality may differ between different methods of placebo administration. Given this was the first study to investigate the role of fear of minor pain within OLP responding, it is important for this finding to be re-examined in future research to ensure this was a reliable finding.

4.4.4. The conflicting role of fear of pain within placebo analgesia

Although understanding the role of personality within OLP and DP analgesia may provide the benefit of matching a more appropriate treatment to an individual based on their personality, the role of fear of pain may provide some confusion within this process. With regards to subjective pain intensity, lower fear of medical pain indicated an increase in placebo analgesia, however, an increase in fear of minor pain increases the likelihood of placebo responding for objective pain tolerance. With subscales of the FPQ-III being negatively and positively associated with OLP responding, it demonstrates there may be some confusion, given it may be the case that participants who score higher on one subscale are more likely to score higher on another subscale. For example, there was a significant moderate positive correlation between fear of medical pain and fear of minor pain within this study, with another study also highlighting positive moderate correlations between fear of pain subscales (Mittinty et al. 2018), suggesting they are somewhat related. To further explain this, if an individual scored higher on fear of minor pain, it may be possible that they are more likely to score higher on fear of medical pain. This suggests that, if the FPQ-III was used as a treatment matching method for choosing the most suitable placebo route, the FPQ-III could present problems. If an individual scores higher on fear of minor pain, they may be more likely to experience an enhanced pain tolerance, however, they are likely to also score higher on fear of medical pain,

suggesting they are also more likely to experience a higher pain intensity. This suggests there may be some conflict with using the FPQ-III to treatment match as it is likely that, whilst enabling an individual to tolerate pain for a longer period of time, they will feel more pain whilst doing so. It is, however, important to consider that this finding may only be in this sample and should be investigated further in the future.

To address this conflict, firstly, it is vital to consider that one finding is for pain intensity and the other is for pain tolerance. This suggests different subscales of the FPQ-III influence pain intensity and pain tolerance in different ways. Importantly, pain tolerance and pain intensity are not independent measurements within this study, with it being possible that the longer an individual tolerates pain for, the more pain they may experience. However, within this study pain tolerance and pain intensity were not significantly correlated; thus, suggesting they may be measuring two unrelated outcomes. This suggests that, if pain tolerance and pain intensity are unrelated, it may be possible for personality-related variables to influence the two outcomes in differing ways. Previous research has also found that headache sufferers experienced a higher level of fear of severe pain and medical pain, although experienced a lower level of fear of minor pain (Hursey and Jacks 1992). This, therefore, suggests that fear of minor pain may influence pain in an opposing direction to fear of medical and severe pain, leading to a potential explanation for why placebo analgesia within the OLP group is influenced in an opposing direction to fear of minor and medical pain.

4.5. Strengths and Limitations

This study confirmed the consistent finding that open-label placebos are effective and added to the understudied area of open-label placebos and the influence of personality. This was the second known study to investigate the role of personality within OLP responding and the first known study to look at many personality-related variables in relation to whether they predict OLP responding. This is an important strength as it highlighted original findings which can lead to useful implications. This study also compared the effectiveness of an OLP to a DP, a comparison made only a small number of times (Barnes et al. 2019; Locher et al. 2017). Given there are inconsistencies within the literature with regards to the effectiveness of an OLP compared with a DP, it is important that additional research was carried out, attempting to clarify any inconsistencies. With deceptive placebos often being viewed as unethical, comparing an OLP and a DP is a very useful way of understanding the relevance of

deception within placebo analgesia; thus, understanding whether it is possible to reduce the ethical issues whilst using placebos.

This study also utilised a novel method of placebo and pain induction within OLP research. The most popular placebo within OLP research appears to be placebo pills (Carvalho et al. 2016; Kaptchuk et al. 2010; Kelley et al. 2012; Sandler and Bodfish 2008; Schaefer et al. 2016), with a placebo cream also being used within a small number of studies (Locher et al. 2017, 2019). However, to our knowledge, an inactive nasal spray has never been used as a placebo within OLP research. This is an important strength within this study as it has highlighted two important factors. Firstly, the OLP is effective, even when the placebo is in a variety of different forms and secondly, this suggests that if open-label placebos do arise within clinical environments, those prescribing the treatment have a range of placebo methods they can choose. With regards to the unique pain induction method within this research, this study is the only known OLP study to use the CPT to induce pain. Other similar research favoured heat pain induction (Locher et al., 2017). With this study using a unique pain induction method and placebo form within the OLP literature, it highlights that open-label placebos are effective for a new type of pain and effective when given using an alternative method to what previous research has shown. Thus, this demonstrates a novel type of pain open-label placebos are effective for relieving and an additional placebo form which may be useful to healthcare providers.

A further strength of this study is that it was conducted in a controlled environment with healthy participants. OLP literature predominantly has focussed on clinical populations which, although this is useful, it is also important to conduct research in a controlled manner to control for many variables which cannot be controlled whilst using a clinical sample. For example, when using a clinical sample all participants are likely to have experienced a medical condition for differing periods of time and it is not possible to confirm that all participants experience the same symptoms to the same extent. Therefore, by exposing participants to the CPT at three degrees Celsius within this study, this removed any uncertainty with regards to whether all participants experience the same painful stimuli. However, research has suggested that placebo effects are more powerful within a clinical sample (Forsberg et al. 2017), suggesting this study may not be generalisable to a clinical sample as patients may benefit from even greater placebo analgesia than what was demonstrated within this study.

A limitation within this research may come from the understanding that all participants were psychology students. As psychology students have a pre-existing background within psychology and are likely to be aware of the placebo effect and, particularly for those in the DP condition, they may have been sceptical if they were receiving a real painkiller and considered that they may have received a placebo. Therefore, the inclusion of psychology students, as opposed to non-psychology students, may have meant participants were more sceptical about the true nature of the placebo.

A further limitation within this study was that the sample size was reasonably small, given several participants were excluded for reaching, or being close to, the ceiling CPT time of 180 seconds. This may have resulted in statistical tests being underpowered. Furthermore, as with many pieces of research, there was an age bias with over 90% of participants used within data analysis being between 18 and 25 years old, raising potential questions as to whether findings can be generalised to those of all ages. A further sample bias may be that only participants who were willing to experience pain participated in this study. As participants voluntarily signed up for this study, all recruitment materials informed participants that the study will involve a painful stimulus which may have led those who are particularly worried about experiencing pain to not participate. Thus, this suggests that this study does not represent those who are particularly worried about experiencing pain or those who are more sensitive to pain. In other words, it is possible to suggest that this study is only representative of those who are willing to experience pain within research. Finally, it is important to consider the role of investigator bias within this study as the researcher was aware which group each participant was in, meaning he may have portrayed unconscious cues to influence participants. However, researcher-participant interaction was minimal with most instructions provided via computer.

A further consideration which must be taken into account within this research is the large quantity of analyses and, therefore, the increased risk of observing a Type 1 error (Ruxton & Beauchamp, 2008; Coolican, 2009). Firstly, regarding the ANCOVAs carried out, planned contrasts were agreed upon before analysis, opposed to post-hoc testing as this reduces the risk of making Type 1 errors (Locher et al. 2017; Ruxton & Beauchamp 2008). In addition, the steps within the multiple regressions and the reference group were pre-defined before the regression analyses took place; therefore, attempting to reduce the risk of a Type 1 error by only carrying out analyses which were of importance within the scope of this study. Furthermore, Coolican (2009) stated that the 1 in 20 likelihood of making a Type 1 error is mostly relevant where data is selected at random. Whereas, where there is a theoretical grounding or previous research supporting the findings, the risk of making a Type 1 error is reduced.

For example, this study found no placebo effects for pain tolerance, however, found significant placebo effects for the OLP and DP for pain intensity ratings, following the very same findings of previous research (Locher et al. 2017). Thus, this suggests that, for two similar studies to find similar results, the risk of a Type 1 error being observed within these findings is relatively low.

Regarding the regression analyses investigating the role of personality-related variables, the risk of a observing a Type 1 error is arguably higher than within the ANCOVAs. The suggested reason for this is the far greater number of statistical tests, and the limited theoretical understanding and research investigating the role of personality on OLP responding. For this reason, the analyses surrounding personality-related variables have been titled exploratory and thus findings are, therefore, preliminary and should be treated with caution.

A suggestion for controlling the likelihood of observing a Type 1 error is to lower the P value, perhaps to 0.01 (Coolican, 2009). To explain this in terms of the findings regarding personality, the only interaction which would continue to be statistically significant, accepting the P value at 0.01, is between the OLP and DP's pain intensity ratings, whilst being moderated by agreeableness. However, given these analyses are exploratory and these findings are preliminary, the P value was maintained at 0.05. Should a more cautious approach have been taken, accepting the P value at 0.01, it may have been possible for this preliminary research to miss an important finding and, thus, create a Type 2 error. For this reason, the advice is as follows; this is the first study to find the relationship between OLP analgesia and personality-related variables, therefore, it is not yet known how generalisable these findings are. Although these findings should be treated with caution, they should, however, be used as guidance for future research attempting to replicate the findings of this study.

4.6. Implications

Open-label placebos have only been compared to deceptive placebos in a small number of studies. However, when they were compared within this study and Locher et al. (2017), it was found that open-label placebos and deceptive placebos are equally as effective as each other within placebo analgesia, with the belief a placebo was a real painkiller failing to add any further effectiveness. In addition, this study and Locher et al. (2017) only found placebo effects with subjective measurements of pain. Research is beginning to suggest that deception may not be necessary within placebo analgesia as receiving a placebo openly creates the same effect as if it was given under the belief that it was a

genuine painkiller. Thus, this study has further added to the literature suggesting that it may be possible to use placebos in an ethical way. By using placebos in an ethical way, it may be possible to use them more often, particularly with a clinical sample. This could, therefore, mean that an ethical placebo could be prescribed and trialled with an individual rather than a genuine drug or painkiller which could potentially save health care providers money.

Given three personality-related variables (agreeableness, fear of minor pain, and fear of medical pain) moderated OLP and DP analgesia in opposing ways, a positive implication which can be taken from this research is the potential to suggest personality testing to discover whether a placebo given openly or deceptively may be more suitable for an individual. With high scores of agreeableness decreasing placebo analgesia within the DP group, but high scores predicting placebo analgesia within the OLP group, measuring agreeableness before deciding whether an OLP or DP may be useful. Therefore, if an individual scored highly on agreeableness, it would be possible to suggest an OLP may be more effective; however, if an individual scored lower on agreeableness, they may be more suited to receiving a placebo deceptively. This concept can also be applied to fear of medical pain, fear of minor pain, and any other personality traits found to predict OLP and DP responding differently in future research.

4.7. Suggestions for future research

Firstly, although this study and Locher et al. (2017) demonstrated that the OLP only produces placebo analgesia for subjective ratings of pain and that the OLP and DP are equally as effective as each other, it is important to reproduce these studies and confirm that these findings are reliable. This is particularly important as there continues to be a relatively small number of studies comparing the effectiveness of the OLP and DP. Furthermore, the known studies which have compared the effectiveness of the OLP and DP have used healthy participants. It is important to compare placebos given openly and deceptively within a clinical sample with patients as research does suggest placebo effects are greater within clinical samples (Forsberg et al. 2017). It also appears that OLP and DP responding are only effective within placebo analgesia, however, not with nausea (Barnes et al. 2019). It is important to confirm whether OLP and DP effectiveness is only similar within placebo analgesia or whether an OLP and a DP share similar effectiveness within other medical conditions.

There is also a need for more research highlighting whether agreeableness, fear of medical pain, and fear of minor pain moderate OLP analgesia and to examine whether these findings are specific to this sample or can be generalised to the greater population. Given research investigating the role of personality within OLP effectiveness is scarce, it is also suggested that more research is carried out with the personality-related variables in this study, to re-examine whether any important findings were missed and, furthermore, whether there are any personality-related variables which were not measured in this study which may also predict the likelihood of responding positively to an OLP. For example, novelty-seeking (Schweinhardt et al. 2009), social desirability (Gelfand, Gelfand, & Rardin, 1965), ego-resiliency (Peciña et al., 2013), and empathy (Darragh et al. 2014) have also been shown to influence DP responding and, therefore, may also have some influence on OLP responding.

A further direction for suggested future research is to understand which type of placebos are most effective within the OLP. Many OLP studies have used placebo pills, with placebo creams and placebo nasal sprays also being shown to be effective to reduce pain or symptoms, even when the true nature of the placebo was known. However, to date, no research has directly compared whether different types of placebos are equally as effective as each other, or whether particular placebo types are more effective when reducing symptoms with the OLP.

Finally, given previous research on placebos has demonstrated that placebo effectiveness may be determined by the social context such as the competence and warmth of the physician (Howe et al. 2017), research should investigate whether the social context influences the effectiveness of an OLP. For example, a possible avenue for future research could be to investigate whether the warmth or competency of the researcher influences OLP effectiveness or whether a rationale for why open-label placebos are effective may be more powerful and believable if given by a seemingly competent researcher. Furthermore, other factors could be considered within OLP research to highlight whether the social context plays a role in its effectiveness such as where the research is conducted; would a doctor's office or medical environment lead to greater OLP effectiveness than a university laboratory? To clarify, it is important to ask questions about whether the social settings and the physician involved in prescribing the treatments can influence the effectiveness of the OLP and question the positive implications this may have on the usefulness of the OLP with patients.

4.8. Conclusion

This study found that open-label placebos and deceptive placebos were both effective for reducing subjective ratings of pain and that open-label placebos and deceptive placebos do not significantly differ in effectiveness. This research, along with a growing body of literature, suggests that the necessity of deception within placebo analgesia should be questioned as it may be possible to use placebos in a more ethical way if given openly.

Furthermore, this was the first known study to investigate the role of many personality-related variables in terms of whether they predict OLP analgesia. Agreeableness, fear of medical pain and fear of minor pain influenced OLP responding in a differing way to DP responding suggesting a 'placebo responder' personality may differ for an OLP and a DP. Positive implications include the suggestion of using personality testing to evaluate whether an individual is likely to respond to an OLP or a DP. However, further research is needed to confirm that personality-related variables do influence OLP analgesia and, furthermore, that open-label placebos and deceptive placebos do share equal effectiveness. Nevertheless, this research raises the possibility of using placebos openly within clinical situations which has the potential of resolving ethical issues of trust between health care providers and their patients.

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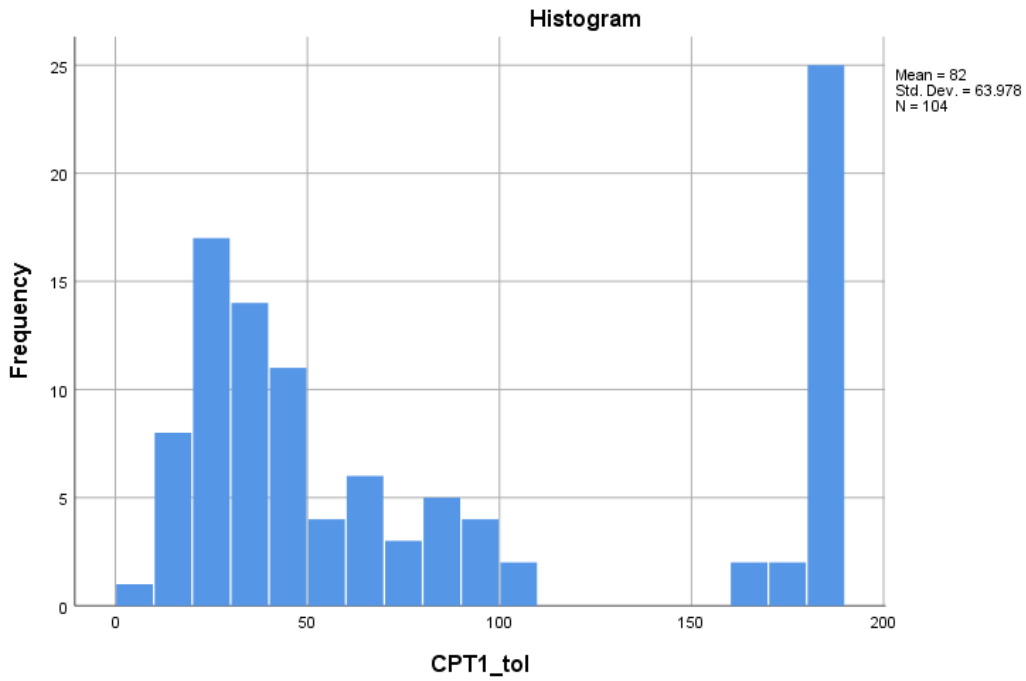
6. Appendix

Appendix 1: *Histogram demonstrating the ceiling effect within baseline pain tolerance.*



Appendix 2: *Information sheet provided to those in the OLP group.*

Placebo Information Sheet

Please read this information sheet carefully.

You will shortly be given a placebo in the form of a nasal spray, however, it will be inactive and will not contain any pain killing properties.

Your researcher will prepare the nasal spray for you and when instructed to, you will be asked to gently put it inside your nostril and give a fast positive spray, pointing the nasal spray towards the top of your nose. You will do this for both nostrils. This may feel slightly uncomfortable and there may also be excess solution which you can remove with a tissue provided. Each nasal spray is disposed of after each use.

There are no known side effects to this nasal spray, however, if you do experience any symptoms of an allergic reaction (rash, itching/swelling, severe dizziness, trouble breathing) seek medical attention promptly.

Although this placebo contains no medication, placebo effects may still be powerful. This means that even when you know you are receiving a placebo, you may still experience the pain relief which an active drug would induce; thus you may still experience pain relief from administering the nasal spray. In previous research, placebos have successfully reduced pain and symptoms of many other medical conditions, even when participants knew they administered an inactive substance (a placebo).

Having a positive attitude towards taking this placebo can improve its effectiveness, however, it is not necessary as pain relief may still be experienced.

Once you have taken the placebo, you will be asked to wait 30 seconds before participating in the second cold pressor test. We politely ask that you stay silent during this 30 second period.

The researcher will now give you a recap of this information sheet and prepare the placebo for use. You will be told when to administer the placebo.

Appendix 3: *Information sheet provided to those in the DP group.*

Painkiller Information Sheet

Please read this information sheet carefully.

You will soon be given a painkiller in the form of a nasal spray. Your researcher will prepare the painkiller for you and when instructed to, you will be asked to gently put it inside your nostril and give a fast-positive spray, pointing the nasal spray towards the top of your nose. You will do this once for both nostrils. This may feel slightly uncomfortable and there may also be excess solution which you can remove with a tissue provided. Each nasal spray is disposed of after each use.

There are no known side effects to this painkiller, however, if you do experience any symptoms of an allergic reaction (rash, itching/swelling, severe dizziness, trouble breathing) seek medical attention promptly.

You will receive an analgesic nasal spray, which contains Lidocaine, the main ingredient used in Stilex (a painkiller commonly used in Switzerland). The nasal spray prevents and treats pain for a small period of time, providing pain relief for various medical procedures which involve a small level of pain. Lidocaine has also been known to relieve chronic pain. The effectiveness of Lidocaine has been proven in several high quality studies carried out worldwide. It usually takes approximately 30 seconds to induce an analgesic effect.

Once you have administered the painkiller, you will be asked to wait 30 seconds before participating in the second cold pressor test. We politely ask that you stay silent during this 30 second period.

The researcher will now give you a recap of this information sheet and prepare the nasal spray for use. You will be told when to administer the nasal spray.

Appendix 4: Descriptive statistics discussion for pain tolerance

As demonstrated in Figure 1, pain tolerance for the NT group is very similar between the baseline and post-treatment CPT. When referring to pain tolerance for those in the OLP and DP groups, both groups experienced an increase in pain tolerance in the post-treatment CPT. However, the SEM error bars do demonstrate that there is a large amount of variance around the means, suggesting although the mean tolerance times are convincing that receiving the placebos may be effective, this may not result in statistically significant differences between groups.