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Personality and placebo responses in non-pain paradigms: Building a Transactional Model of Placebo Responding

By Margot Darragh
Abstract

In a modern healthcare environment burdened by symptomatic and mental-health related ailments, the placebo effect may represent a useful clinical tool. However, with the bulk of research to date conducted in pain contexts, more exploration is needed into the power of the placebo in other settings. Similarly, insights into the type of person most likely to respond to placebo treatments arise predominantly from pain contexts, and it is not known whether the same personalities are responsive in non-pain settings.

This research programme aimed to address these two limitations in the extant literature by investigating: (1) What are the capabilities of placebo suggestion outside the context of pain; and (2) Which personality characteristics predict placebo responses in these other contexts. After a systematic review of the placebo personality literature, three experimental studies were conducted to investigate placebo effects in the context of: (1) acute psychosocial stress recovery \((N = 60)\); (2) histamine-induced inflammatory skin reactions \((N = 48)\); and (3) a take-home placebo treatment for stress, anxiety, and depressive symptoms arising from the demands and challenges of everyday life \((N = 77)\). All three studies employed suggestive placebo protocols and used physically healthy samples.

Results extend findings from prior investigations and offer several novel, incremental findings to the extant placebo literature. Suggestive placebo protocols were shown to enhance physiological recovery from acute psychosocial stress; to reduce the experience of itch; and to ameliorate symptoms of stress, anxiety and depressive symptoms in a naturalistic setting. In answering the second research question, the Transactional Model of Placebo Responding (TMPR) was developed to provide a framework for understanding how personality traits might interact with environmental cues to influence placebo responses. Specifically, the model proposes that there are two facets of responsiveness - inward orientation and outward orientation - which may respond to different environmental cues.

The findings from this research programme offer both empirical and theoretical contributions to the placebo literature. More research is needed to replicate and extend results; however, once properly refined and tested, the TMPR may offer utility in predicting who might be responsive to placebo treatments, thus maximising the placebo’s potential as a clinical tool.
Acknowledgements

First and foremost, I would like to express my gratitude to my principal supervisor, Nathan Consedine, who motivated, challenged, and inspired me throughout this entire experience. I consider myself very fortunate to have been able to benefit from your aptitude and love of mentoring and teaching. I am grateful to have had a supervisor who has both the ‘stick’ and the ‘carrot’ in their arsenal and knows when and which one to use. Thank you for providing me with care and empathy when I needed it but reining me in when I got a little carried away. I never stopped learning from you and I will miss your regular presence in my life.

I would also like to thank my co-supervisor Roger Booth for his enthusiasm and contributions to my research and in particular for having one eye on the details while keeping the other eye on the big picture.

I am also grateful for the guidance and support I received from the faculty and staff of the Health Psychology Department during my masters and doctoral journey. From my first undergraduate lecture of Health Psych 365 I knew that this was ‘it’, and I am grateful that there was a programme that enabled me to pursue this area of study.

Thank you to everyone who contributed to my research. Special thanks to my research participants, who gave up their time and allowed me to experiment on them, as well as my research assistants, who took over the considerable burden of running experimental protocols so that I could focus my attention on other aspects of my doctoral research.

Thank you to my friends for your support and patience during this journey. There were many ups and downs along the way, and everyone got a chance to listen to me bleat about my research or my thesis at least once. Thank you to my whole family, but special thanks to my big sister who was also on a PhD journey a year ahead of me and thus able to provide support and guidance all along the way. Special thanks also to my Mum for not only the proofreading, but for your unwavering interest in my thesis topic as well as my whole academic experience. Dad, you never got to read my thesis, but I am sure you would be proud of me.

Last but not least, thank you to my Health Psychology colleagues. I have truly relished this journey, which is in no small part due to being surrounded by ‘kindred spirits’. I was especially grateful to have you Fiona, going through the process at the same time as me. Doing a PhD is a rollercoaster and being able to ride it with friends made all the difference.
# Table of Contents

Abstract ........................................................................................................................................ ii
Acknowledgements .................................................................................................................. iii
Table of Contents .................................................................................................................... iv
List of Papers (published and in submission) ........................................................................ vii
List of Figures .......................................................................................................................... viii
List of Tables ............................................................................................................................ ix
Co-authorship forms and permissions ................................................................................... x

## 1. OVERVIEW

1.1. Background: the health context ....................................................................................... 1
1.2. The research questions ..................................................................................................... 3
1.3. Overview of research methodology .................................................................................. 3
1.4. Thesis structure ................................................................................................................. 4

## 2. THE PLACEBO EFFECT

2.1. Background ....................................................................................................................... 7
2.2. Defining the placebo phenomenon ................................................................................... 8
2.3. Research approaches ....................................................................................................... 10
   2.3.1. The conditioning paradigm ...................................................................................... 11
   2.3.2. The expectancy/expectation paradigm .................................................................... 11
2.4. Mechanisms of placebo expectancy ................................................................................ 12
   2.4.1. Response expectancies ........................................................................................... 12
   2.4.2. Learning processes ................................................................................................ 12
   2.4.3. Cognitive, behavioural, and emotional changes ...................................................... 13
   2.4.4. Neurobiological mechanisms ................................................................................. 14
2.5. The placebo suggestion literature .................................................................................... 15
   2.5.1. Suggestive placebo protocols in patient and healthy samples ............................... 15
   2.5.2. The prolific placebo analgesia paradigm: a limitation of the literature ................. 16

## 3. THE PLACEBO EFFECT OUTSIDE THE PAIN PARADIGM

3.1. The placebo effect in the context of physiological recovery from psychosocial stress ....... 19
   3.1.1. Abstract .................................................................................................................. 19
   3.1.2. Introduction ........................................................................................................... 20
   3.1.3. Methods ................................................................................................................ 21
   3.1.4. Measures ............................................................................................................... 24
   3.1.5. Statistical analysis ................................................................................................. 24
   3.1.6. Results .................................................................................................................. 25
   3.1.7. Discussion ............................................................................................................. 27
3.2. Interim commentary: from psychosocial stress to inflammatory skin reactions .......... 29
3.3. The placebo effect in the context of inflammatory skin reactions ................................ 31
   3.3.1. Abstract ................................................................................................................ 31
3.3.2. Introduction

3.3.3. Materials and Methods

3.3.4. Results

3.3.5. Discussion

3.4. Interim commentary: from the laboratory to a naturalistic setting

3.5. The placebo effect in the context of stress, anxiety, and depressive symptoms in a non-laboratory setting

3.5.1. Abstract

3.5.2. Introduction

3.5.3. Method

3.5.4. Measures

3.5.5. Results

3.5.6. Discussion

3.5.7. Conclusion

3.6. Summary: suggestion-induced placebo effects in non-pain paradigms

4. THE POSSIBLE ‘PLACEBO-PRONE’ PERSONALITY

4.1. Personality

4.2. Systematic literature review

4.2.1. Background

4.2.2. Search procedures

4.2.3. Results

5. CONCEPTUALISING PLACEBO RESPONSIVENESS

5.1. A new conceptualisation of placebo responding

5.1.1. Abstract

5.1.2. Introduction

5.1.3. A conceptualisation of placebo responsiveness

5.1.4. A Transactional Model of Placebo Responding (TMPR)

5.1.5. Clinical applications

6. PERSONALITY PREDICTORS IN NON-PAIN CONTEXTS

6.1. Personality predictors in the context of stress recovery

6.1.1. Abstract

6.1.2. Introduction

6.1.3. Methods

6.1.4. Experimental procedure

6.1.5. Measures

6.1.6. Statistical analysis

6.1.7. Results

6.1.8. Discussion

6.1.9. Limitations and future directions

6.2. Interim commentary: personality predictors of responding in non-pain contexts

6.3. Personality predictors of responding in the context of inflammatory skin reactions
List of Papers (published and in submission)

<table>
<thead>
<tr>
<th>Ch.</th>
<th>Published</th>
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## List of Figures

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<th>Ref</th>
<th>Figure legend</th>
<th>Pg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Overview of the doctoral research programme, with grey shading indicating papers addressing the placebo personality research question.</td>
<td>6</td>
</tr>
<tr>
<td>3.1</td>
<td>Experimental protocol for Phase I and Phase II with shaded boxes indicating tasks carried out by the researcher (all others administered by the RA).</td>
<td>22</td>
</tr>
<tr>
<td>3.2</td>
<td>Log high frequency ms$^2$ auto regression spectrum HRV by Group from Recover 1 to Recover 2 (error bars are standard error of the mean) controlling for time of day.</td>
<td>26</td>
</tr>
<tr>
<td>3.3</td>
<td>Mean HR in beats per minute by Group from Recover 1 to Recover 2 (error bars are standard error of the mean) controlling for time of day.</td>
<td>27</td>
</tr>
<tr>
<td>3.4</td>
<td>Overview of study design.</td>
<td>34</td>
</tr>
<tr>
<td>3.5</td>
<td>Overview of the recruitment and enrolment process.</td>
<td>34</td>
</tr>
<tr>
<td>3.6</td>
<td>Average reported itch at 1, 3, 5 and 7 minutes post-histamine administration by session (control versus treatment). Error bars are standard error of the mean.</td>
<td>40</td>
</tr>
<tr>
<td>3.7</td>
<td>Average weal size in the control session and treatment session by Group. Error bars are standard error of the mean.</td>
<td>41</td>
</tr>
<tr>
<td>5.1</td>
<td>The umbrella construct ‘permeability’, comprising the two dimensions of inward and outward orientation.</td>
<td>71</td>
</tr>
<tr>
<td>5.2</td>
<td>Transactional Model of Placebo Responding in which the two facets of permeability (inward/outward) represent predispositions to respond to environmental cues, with potentially appropriate cues and possible pathways described.</td>
<td>73</td>
</tr>
<tr>
<td>6.1</td>
<td>Flow chart of the study recruitment, enrolment, participation including any necessary exclusions.</td>
<td>80</td>
</tr>
<tr>
<td>6.2</td>
<td>Experimental protocol for Phase I and Phase II with tasks (unbroken lines) and measures (dashed lines). Shaded boxes indicate tasks carried out by the researcher (all others administered by RA). BQ = baseline questionnaire; S1 – S6 = self-reported stress measures.</td>
<td>81</td>
</tr>
<tr>
<td>7.1</td>
<td>A photo of the placebos used in Experiment III: ‘oxytocin’ and ‘serotonin’ treatment compounds delivered in an intranasal spray.</td>
<td>109</td>
</tr>
<tr>
<td>7.2</td>
<td>Change in symptoms of depression (CES-D), anxiety (CSAQ) and stress (PSS) by Group (Control, Serotonin, Oxytocin) with Day 1 (pre-treatment) subtracted from Day 5 (post-treatment) so that negative values indicate a reduction.</td>
<td>119</td>
</tr>
<tr>
<td>7.3</td>
<td>Group (Serotonin and Oxytocin) by trait (low and high BAS) in change in depressive symptoms (Day 5 minus Day 1) relative to the control group’s change. Error bars are standard error of the mean.</td>
<td>120</td>
</tr>
<tr>
<td>7.4</td>
<td>Group (Serotonin and Oxytocin) by trait (low and high BIS) in change in depressive symptoms (Day 5 minus Day 1) relative to the control group’s change. Error bars are standard error of the mean.</td>
<td>120</td>
</tr>
<tr>
<td>7.5</td>
<td>Group (Serotonin and Oxytocin) by trait (low and high BAS) in change in anxiety symptoms (Day 5 minus Day 1) relative to the control group’s change. Error bars are standard error of the mean.</td>
<td>121</td>
</tr>
<tr>
<td>7.6</td>
<td>Group (Serotonin and Oxytocin) by trait (low and high BIS) in change in anxiety symptoms (Day 5 minus Day 1) relative to the control group’s change. Error bars are standard error of the mean.</td>
<td>122</td>
</tr>
</tbody>
</table>
# List of Tables

<table>
<thead>
<tr>
<th>Ref</th>
<th>Table legend</th>
<th>Pg.</th>
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<tbody>
<tr>
<td>3.1</td>
<td>Between group differences in demographics, health behaviours, session time, and outcome variables pre and post manipulation; with means, standard deviations, degrees of freedom, test statistics, significance values and effect sizes.</td>
<td>25</td>
</tr>
<tr>
<td>3.2</td>
<td>Results of baseline between group tests with test statistics, degrees of freedom, significance levels and effect sizes.</td>
<td>38</td>
</tr>
<tr>
<td>3.3</td>
<td>Results of repeated measures ANCOVAs testing for main effects of Session (placebo effects) and Group (order of session) while controlling for the presence of allergies (Allergies) and changes in negative mood (Negative Mood).</td>
<td>39</td>
</tr>
<tr>
<td>3.4</td>
<td>Tests for baseline differences between the groups in demographic, health, and outcome variables; as well as tests for placebo effects on outcome variables.</td>
<td>53</td>
</tr>
<tr>
<td>3.5</td>
<td>Results of Independent sample t-tests comparing the serotonin and oxytocin groups in adherence to the regime, as well as the perceived effectiveness of the treatment.</td>
<td>54</td>
</tr>
<tr>
<td>4.1</td>
<td>Systematic search exclusion criteria with reasons for each criterion.</td>
<td>63</td>
</tr>
<tr>
<td>4.2</td>
<td>Summary of evidence for those constructs empirically linked to placebo responding with overall number of studies (k), pooled sample sizes (pooled N), the proportion demonstrating a relationship with personality, and the condition or context in which the placebo manipulation took place.</td>
<td>64</td>
</tr>
<tr>
<td>6.1</td>
<td>Results of baseline between group tests (sex, ethnicity, age, health behaviours and session time), and tests for placebo effects (repeated measures ANOVAs) in reported stress, HR and HRV, with means, standard deviations, degrees of freedom, test statistics, significance values and effect sizes.</td>
<td>86</td>
</tr>
<tr>
<td>6.2</td>
<td>Correlations between personality traits and outcome variables. Pearsons (r) and Spearman’s (rho) tests used depending on violation of normality. Relationships between the personality trait and the outcome variable by group, with between-group comparison of r / rho coefficients via z statistics and significance values.</td>
<td>89</td>
</tr>
<tr>
<td>6.3</td>
<td>Results from a one-step forced entry multiple regression for self-reported serotonin effects, and two three-stage forced entry multiple regressions for change in HR and Recover2 HRV.</td>
<td>90</td>
</tr>
<tr>
<td>6.4</td>
<td>Pearson’s product moment correlations between predictor and each outcome variable: the difference in itch from control to treatment sessions, at 1, 3, 5, and 7 minutes, and weal size, with control session values subtracted from treatment session values.</td>
<td>102</td>
</tr>
<tr>
<td>6.5</td>
<td>Pearson’s product moment correlations among trait variables.</td>
<td>103</td>
</tr>
<tr>
<td>6.6</td>
<td>Three step forced entry regressions for each outcome variable: the difference in itch from control to treatment sessions, 1, 3, 5, and 7 minutes, and weal size. Group entered as step 1, Traits entered in step 2, and a Group*Trait interaction term entered in step 3.</td>
<td>105</td>
</tr>
<tr>
<td>7.1</td>
<td>Tests for baseline differences between the groups in personality, demographic, health and outcomes; and placebo effects on outcome variables, with means, standard deviations, test statistics, and significance levels.</td>
<td>118</td>
</tr>
</tbody>
</table>
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3.2. The placebo effect in the context of inflammatory skin reactions.

**Nature of contribution by PhD candidate**

Conception and design of study, development and implementation of protocol, analyses, wrote the bulk of the manuscript.

| Extent of contribution by PhD candidate (%) | 70% |

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S.I. A new model of placebo responding.

Nature of contribution by PhD candidate: Conducted systematic literature review, critique and analyses, formulated the model and wrote the bulk of the manuscript.

Extent of contribution by PhD candidate (%): 70%

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6.2. Personality predictors of responding in the context of inflammatory skin reactions.

| Nature of contribution by PhD candidate | Conception and design of study, development and implementation of protocol, analyses, wrote the bulk of the manuscript |
| Extent of contribution by PhD candidate (%) | 75% |

**CO-AUTHORS**

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<td>Roger J Booth</td>
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<td>Nathan S Considine</td>
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**Certification by Co-Authors**

The undersigned hereby certify that:

✦ the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and

✦ in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

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1. OVERVIEW

1.1. Background: the health context

The modern medical industry has changed the healthcare landscape. Innovations in science and technology have yielded life-changing ways to treat and control disease, combat infection, and increase life expectancy; however, the outlook is not all good. Mental health-related conditions such as depression and anxiety are rampant [1]; work-related stress is now a major public-health problem [2]; psychosomatic and medically unexplained illnesses are burdening health systems; and primary care is plagued by symptomatic and overmedicated individuals [3, 4]. Treating such costly, pervasive, debilitating, and potentially long-term conditions has become a critical challenge.

In primary care, symptom-generated health complaints are burdening the health system and the economy. There is a clear relationship between the experience of symptoms, visits to the doctor, medicine use, and days absent from work through sickness [5]. Symptomatic conditions are clearly an issue for the healthcare system; however, many symptom-related complaints are not associated with identifiable organic pathology. For example, ‘medically unexplained’ functional disorders represent a significant presence in primary care and generate high usage of healthcare resources [3, 4]. Conditions of this kind can be challenging to treat because if there is no identifiable pathogen, the pharmacological approaches that are designed to target and destroy pathogens are relatively ineffective.

Other conditions which are pervasive in primary care may have identifiable biological causes but can still be difficult to treat because it is psychosocial factors rather than disease processes that are influencing the ongoing experience and reporting of symptomology. For example, chronic idiopathic urticaria (hives) generates high rates of healthcare utilisation, and factors such as stress and anxiety can contribute to and exacerbate this condition [6]. In treating chronic skin conditions, the use of steroids or other medications for long time periods can be harmful [7, 8] and it would be useful to have adjunctive and alternative treatment options.
Similarly, successfully treating mental health-related ailments such as stress, anxiety, and depression can also be troublesome. Not only are such conditions pervasive [9, 10], but there are potentially harmful side effects associated with long-term pharmacological treatments [11, 12]. At least in some samples, taking antidepressants may not deliver any benefit over no treatment, in the long term [13], and it has been suggested that doctors may be prescribing antidepressants unnecessarily [14]. Again, the availability of some sort of supplemental treatment alternative would be useful for practitioners.

The increases in lengths and rates of prescriptions observed in recent years [15, 16] may be indicative of a wider problem: the overuse of medication; however, the blame for this issue does not rest solely with physicians [17], as patient behaviour and demand for medicinal approaches [18] have been found to contribute to over-prescribing [19, 20]. Patients appear to need to feel like they are receiving medicine, even if there is no pill for what ails them. Thus, it may be that a return to the art of medicine, rather than the act of prescribing pharmaceuticals [21, 22], is needed.

Since the 1950s, the method of determining a treatment's effectiveness has been by the efficacy of its specific pharmacological ingredients. Perhaps as a result of this legacy, the contribution of the therapeutic healing ritual which medicine was traditionally delivered with may have become somewhat neglected [23]. This 'non-specific' component of treatment can deliver substantial value, however, as documented by the placebo effect [24], in which therapeutic benefits are derived from treatments which do not contain ingredients capable of impacting the ailment in question [23, 25]. In the absence of pharmacologically active agents, placebo treatments reflect the power of the healing ritual [26], the psychosocial context surrounding treatment [22], and an individual's beliefs and expectations [27]. The ability to respond to the mere suggestion of benefit may represent a type of endogenous healthcare system [28, 29].

Thus, placebo treatments may be a possible life raft for our flailing health system by offering an appropriate substitute for drugs in some situations and a useful supplement to be leveraged in others. Placebo treatments may offer adjunctive and bridging treatments at lower costs, and without the risks of iatrogenic harm or overmedicating patients who have chronic and psychologically-influenced conditions. However, before the power of the placebo can be properly harnessed for clinical benefit, there are questions that need to be answered.
1.2. The research questions

This thesis details a programme of doctoral research which is contextualised within the overarching aim of harnessing the placebo effect as a means of assisting with the treatment of pervasive and symptomatic conditions. The following chapters will describe how the majority of studies that investigate the placebo effect do so in the context of experimentally-induced pain, so there is a need to broaden research attention beyond this particular context. Similarly, insights into the type of person most likely to respond to placebo treatments arise predominantly from pain contexts, and it is not known whether the same personalities are responsive in non-pain settings. To address this, two research questions were investigated concurrently: (1) What are the capabilities of placebo suggestion outside the context of pain; and (2) Which personality characteristics predict placebo responses in these other contexts.

1.3. Overview of research methodology

These two research questions were investigated in parallel by way of four studies (Figure 1.1) summarised as follows: (1) a systematic review and critique of the extant placebo personality literature; (2) an experimental study investigating the placebo effect in the context of physiological recovery from acute psychosocial stress, and the personality predictors of placebo responses in this context; (3) an experimental study investigating the placebo effect in the context of inflammatory skin reactions, and the personality predictors of this response; and (4) an experimental, non-laboratory study investigating the personality predictors of responding to two take-home placebo treatments for the alleviation of stress, anxiety, and depression. This final study aimed to integrate the two research questions by testing a new conceptualisation of the possible ‘placebo personality’ (the Transactional Model of Placebo Responding), in which different types of people might respond to different contextual cues.

All three experimental studies employed randomised and controlled designs, so that ‘true’ placebo effects could be detected (see Chapter 2.2). Physically healthy, non-patient populations were used for each experimental study (see Chapter 2.5.1). As shown in Figure 1.1, two empirical reports
were produced from each of the three experimental studies, one focussing on the demonstration of the placebo effect on outcomes beyond pain and the other describing personality predictors of responding in that context. Thus, there are data overlaps between each pair of papers, necessarily arising from using the same sample of participants and the same general procedures. These overlaps were consistently disclosed during the submission and peer-review process. Because adapting published and copyrighted articles is problematic, the articles are included as final word versions of the published papers and thus there may be some slight repetition in the methods sections.

1.4. Thesis structure

As described above, the two research questions were investigated in parallel, with each of the three experimental studies investigating both placebo effects in contexts other than experimental pain, as well as personality predictors of these placebo responses. However, in order to present a cohesive narrative, this doctoral thesis is organised by addressing the two questions in sequential sections. The investigation into placebo effects outside the pain paradigm is presented first, followed by analyses seeking to identify personality predictors of responsiveness second, as detailed below.

Chapter 1 (above) provides an overview of the health context within which this research programme originated, focussing on why the placebo effect matters in the modern health environment. The research question, the methodology employed, and the four studies that were conducted to investigate this question are then described.

Chapter 2 presents an overview of the placebo effect by providing a brief summary of the background to this field of research, defining key concepts and acknowledging important methodological considerations. It then summarises the main research approaches and mechanisms of placebo action before describing the paradigm within which this research programme was conducted.

Chapter 3 address the first research question by presenting three papers investigating suggestion-induced placebo effects in the contexts of stress recovery (3.1), inflammatory skin reactions (3.3), and stress, anxiety and depressive symptoms (3.5).

Chapter 4 details investigations into the second research question by considering the concept of personality (4.1) and then presenting a systematic review (4.2). This review provides an overview of
the current state of the literature while highlighting two key limitations, which are then addressed in the following chapters.

In Chapter 5 the first limitation identified in the literature review, the lack of theoretically-driven research, is addressed with a paper outlining a new conceptualisation of placebo responding: the Transactional Model of Placebo Responding.

Chapter 6 then addresses the second limitation of the literature, the lack of research into personality predictors of responding in non-pain paradigms. Two empirical papers are presented detailing the personality predictors of placebo responding in stress recovery (6.1) and inflammatory skin reactions (6.3).

Chapter 7 presents the final paper in which the two-faceted Transactional Model of Placebo Responding is directly tested by manipulating environmental cues (treatment descriptors) in the context of two take-home placebo treatments for the alleviation of naturalistic stress, anxiety and depressive symptoms.

Chapter 8 provides an overall Discussion chapter that integrates results documented within the thesis by considering the empirical, theoretical and clinical implications of the findings as well as a section on limitations and possible future research directions.

Finally, in conclusion, Chapter 9 summarises the overall research programme and the content presented within this thesis.
Doctoral research commencement
Development of the two research questions:
1) What are the capabilities of placebo suggestion outside the context of pain; and
(2) Which personality characteristics predict placebo responses in these other contexts?

Systematic literature review
A review and critique of the extant ‘placebo personality’ literature.


Experiment I
The placebo effect in the context of psychosocial stress recovery (UAHPEC Ref: 8702)

Paper 2: *Placebo ‘serotonin’ increases heart rate variability in recovery from psychosocial stress.*

Paper 3: *Investigating the ‘placebo personality’ outside the pain paradigm.*

Experiment II
The placebo effect in the context of inflammatory skin reactions (UAHPEC Ref: 010563)

Paper 4: *The placebo effect in inflammatory skin reactions: The influence of verbal suggestion on itch and weal size.*


Experiment III
The placebo effect in the context of alleviating naturalistic stress, anxiety, and depressive symptoms while testing the Transactional Model of Placebo Responding (UAHPEC Ref: 010757)

Paper 6: *A take-home treatment can reduce stress, anxiety, and depressive symptoms in a non-patient population.*


Figure 1.1. Overview of the doctoral research programme, with grey shading indicating papers addressing the placebo personality research question.
This chapter provides an overview of the placebo phenomenon (2.1), with the relevant methodological considerations and key terms described and defined (2.2), before presenting a summary of the two main placebo research approaches (2.3) and some key mechanisms of placebo effects (2.4). Then, a brief review of the placebo suggestion paradigm, in which this research programme was conducted (2.5), is offered as an introduction to the first research question (Chapter 3).

2.1. Background

While enjoying prominence in modern health research, the placebo effect is not a new phenomenon. The use of inert substances in therapeutic healing rituals is an ancient practice [29, 30] that was carried out to provide benefit to ailing individuals long before the advent of pharmacology [24, 31]. Thus, placebo treatments used to be embedded in standard medical practice [23, 32] until the 1950s, when they were commandeered for use in clinical trials and became the gold standard for determining the efficacy of drug treatments [23, 33]. While this had the effect of relegating the placebo to being an ‘inert’ treatment, results from these trials paradoxically revealed that, in some instances, patients randomised to placebo control groups could derive as much benefit as those in the ‘active’ treatment conditions [24]. A seminal publication in 1955, *The Powerful Placebo*, described how placebos could be effective in a range of conditions [34], thus heralding a new field of scientific enquiry into the placebo effect.

The flames of interest in this phenomenon were fanned when the power of the placebo was demonstrated in surgical contexts, with a couple of landmark studies revealing that patients undergoing placebo surgeries had the same post-operative improvement as the ‘real’ treatment group [35, 36]. Placebo treatments, it appeared, could at least make patients *think* they were experiencing improvements. Then, in the 1970s, work investigating the possible mechanisms of the placebo effect revealed that placebos could activate endogenous pain regulation systems [37], providing perhaps the first real evidence that placebos exert effects on human physiological processes [38] and spawning
the now massive field of placebo analgesia research. Over the following decades, scientific investigations continued to explore the power and capabilities of the placebo, and there is now evidence that placebos can influence neurobiological systems, modulate physiological function, and produce clinically significant outcomes [39-47]. Today the placebo effect is generally acknowledged as a genuine psychobiological phenomenon [29]; however, this achievement did not come without its share of doubt and criticism.

At the turn of the 21st century, as the placebo phenomenon gained momentum, serious questions were raised regarding the capacity of placebo treatments to produce clinically meaningful effects and exert real changes on health outcomes [48-50]. A meta-analytic review published in the New England Journal of Medicine in 2001 [49] suggested that rather than powerful, the placebo might instead be powerless, concluding that the placebo effects were only validated for self-reported improvements in a limited range of contexts [49]. This position was maintained for several years, with a follow-up review also casting doubt on the clinical utility of placebo treatments [51].

However, during this period another meta-analysis also investigating the validity and size of the placebo effect revealed, importantly, that factors such as study design and the condition being treated have a significant impact on the detection and size of placebo effects [52]. From this arose the identification of some important conceptual and methodological considerations, as described in the next section.

### 2.2. Defining the placebo phenomenon

The placebo literature is large and heterogeneous, with no real consensus around the ‘correct’ nomenclature [29, 53, 54]. For this reason it is important to clarify and define key terms, as well as consider some contributing methodological factors.

Placebo is a Latin term meaning *I shall please* [55], reflecting the early role of the placebo as a treatment given to appease patients rather than to cure a medical condition [31]. Traditionally, placebos are known as medicinal tools without the actual medicine, such as pills containing only sugar, lactose or starch, injections containing nothing but saline, and ointments containing only moisturising agents. Given the lack of pharmacological ingredients, placebos are often defined as an
inert treatment [56]; however, with evidence that placebos can generate real effects, describing placebos as ‘inert’ is paradoxical [57].

To overcome this issue, some have shifted the emphasis away from the placebo itself, using the term ‘meaning response’ to highlight that in responding to a placebo an individual is in fact responding to what the treatment means [58, 59]. Similarly, placebos have been described in terms of symbols [60] and as signals that convey information, with changes arising from placebo treatments being an effect of the psychosocial context within which they are administered [22, 61, 62]. While such conceptualisations can be useful in thinking about why placebos may ‘work’, for the purposes of this thesis a placebo will be defined as a ‘substance, given in the guise of active medication, but which in fact has no pharmacological effect on the condition being treated’ [63 p. 238]. While placebos are not necessarily limited to the medical arena, at its core the placebo is a health tool, administered for the alleviation of symptoms or noxious stimuli [53].

Two further terms which require definition are ‘placebo response’ and ‘placebo effect’, which, while sometimes used interchangeably, have an important methodological distinction [64]. A placebo response should refer to the changes in an individual after administration of a placebo [53], while a placebo effect is a group effect [29], which can only be properly ascertained by the use of a control group or condition so that artefacts can be ruled out [33, 39, 65, 66]. For example, factors such as regression to the mean [67], the natural fluctuations or progression of an illness [68, 69], patient response biases [70, 71], or perceptual biases such as false positive errors [72] can give the appearance of a placebo effect. A ‘true’ placebo effect [73] therefore refers to the psychobiological processes arising from the administration of a placebo treatment, rather than from statistical artefacts or other confounds [25, 47, 74].

A related issue, the putative power of the placebo, is one that has received considerable attention but that is not easily answered, as there is no one placebo effect and effect sizes vary widely [52, 64]. One source of heterogeneity in this area is the different sources of data contributing to the overall placebo literature. That is, a substantial body of evidence arises from responses observed in placebo control arms of clinical drug trials [75]; however, such findings may not yield a true indication of the magnitude of the placebo effect because such studies are not actually designed to investigate the placebo phenomenon [29]. In drug trials it is the efficacy of a particular pharmacological agent which is being tested, whereas in testing for placebo effects the active agent is a patient’s
expectations and/or the psychosocial context surrounding treatment [22, 26, 27]. When investigating placebo effects these components should be present but in drug trials they often are not [75].

Consistent with this distinction, effect sizes vary depending on whether the placebo effect is being specifically investigated or whether placebo responses are observed incidentally [25, 76]. For example, a meta-analysis revealed a larger mean effect size in studies investigating the placebo effect in the context of pain ($d = .95$), than in drug trials for analgesic agents where placebos served as the control ($d = .15$) [77]. Thus, in drug trials the reported placebo effects can be underestimated [22]; however, studies that investigate the placebo effect without appropriate controls, a particular problem in some earlier work [50, 69], may erroneously attribute experimental artefacts to the placebo effect [33, 39, 65, 66]. Therefore, placebo effects can be both underestimated and overestimated, depending on the study design and purpose.

In order to properly investigate the placebo effect, a control condition is needed as well as the presence of the cues and signals necessary to induce expectations of therapeutic benefit [78]. Placebo treatments can be compared to drug or other interventions to determine the relative efficacy of a placebo or to assess effects arising from the act of taking a treatment (regardless of the ingredients). However, when investigating the power of a placebo treatment to produce particular effects, ideally the placebo condition is treated as the intervention and compared to a no-treatment (natural history) control condition [79].

### 2.3. Research approaches

Researchers often distinguish between two broad pathways by which the administration of a placebo can lead to psychobiological changes: (1) conditioning and (2) expectancy [80]. While sometimes treated as two distinct mechanisms of placebo action, there is considerable difficulty in separating the contributions of these two pathways to placebo-induced changes [53]. For example, the acquisition of expectations can take place through learning; cognitive expectations play a role in learning protocols [53, 81, 82]; and the two may interact with each other to mediate or block placebo effects [53, 83]. Thus, the view that conditioning and expectancy offer two separate mechanisms of placebo effects, and the pitting of one against the other as competing forces in mediating placebo effects, is problematic [53, 64].
Therefore, rather than *mechanistic* pathways of placebo effects, conditioning and expectancy may be better conceptualised as two research approaches: as a means of differentiating the paradigm within which a researcher operates; and as the methods and procedures used to generate a placebo effect. While they might not always be distinct, the adoption of a particular paradigm draws a methodological line in the figurative sand and facilitates the management of a vast and complex literature. The two research approaches are broadly outlined next.

### 2.3.1. The conditioning paradigm

In conditioning protocols, an individual learns through an associative learning process that a certain stimuli (e.g., a placebo pill) is related to the alleviation of noxious symptoms (e.g., pain) [84]. This kind of learning can be created in experimental settings with classical conditioning protocols [e.g., 83, 85, 86-89] such as the repeated pairing of a placebo with the surreptitious reduction of painful stimuli before administering the placebo alone [88]. The subsequent experience of reduced pain when the placebo is administered alone is thought to occur because the individual has learned an association between the placebo and a reduction in pain. A number of different learning protocols have been employed in placebo research to demonstrate effects on cardiovascular and respiratory system activity, a range of immune parameters, and in experimentally-induced pain [45, 90-92].

### 2.3.2. The expectancy / expectation paradigm

In placebo research, expectations are defined as ‘the expected magnitude of a symptom or condition, or the perceived likelihood of an outcome’ [25 p. 571]. The basis of the expectancy pathway is that patients respond to placebo treatments because they *expect* to experience benefit or change [53]. Expectations can be explicit or implicit [81] and expectancy can be manipulated to generate different levels of certainty about outcomes, with differing effects [75, 93, 94]. Expectations can be created by observing others [95] or by learning from prior experience [61]. More explicitly, verbal suggestion can be used to generate expectations about particular outcomes. For example a placebo treatment (e.g., a pill or cream) can be administered with the suggestion that it will result in the alleviation of noxious stimuli (e.g., pain or other symptoms) [86, 91, 96].

This doctoral research programme was conducted within an expectancy paradigm in which explicit verbal suggestion was used to create expectations about outcomes. As such, expectations are


treated as cognitive, conscious processes [29, 53, 81]. As no conditioning protocols were employed, discussion of conditioning paradigms will not be considered further.

While investigating the mechanisms of placebo action is not the aim of this research programme, to facilitate later discussion some key mechanisms by which expectancy-based placebo protocols may exert effects are described next.

2.4. Mechanisms of placebo expectancy

There are thought to be several mechanisms of placebo effects [25, 29, 33, 92, 97, 98] and despite the complexities involved in separating or delineating the relative contributions of different mechanisms, it is still worth briefly outlining some key pathways of placebo action: (1) response expectancies, (2) learning processes, (3) cognitive, behavioural and emotional changes, and (4) neurobiological pathways.

2.4.1. Response expectancies

A theory of expectancy that has been applied to the placebo phenomenon is Response Expectancy Theory [82] in which response expectancies can generate both volitional (e.g., motor control) and non-volitional responses (e.g., pain, arousal) via mediated (e.g., behaviour) or unmediated pathways. For example, an unmediated response can occur when the expectation of feeling worried leads directly to the emotional state of being worried. In the context of placebo effects, the suggestion that a placebo treatment will reduce anxiety can lead directly to a change in that emotional state. Response expectancies about some indices of physiological function which have direct subjective correlates, such as autonomic arousal (fear, anxiety) can also have ‘immediate’ effects; however, other aspects of physiological function, without subjective concomitants, may require mediating pathways [82, 99]. In sum, response expectancies can operate through both unmediated and mediated pathways to generate changes in an individual’s experience.

2.4.2. Learning processes

While cognitive expectations may be a central component of forming placebo responses [25, 81, 92, 100], it has also been suggested that learning may underpin expectancy effects [61]. For example, an
analgesic response after taking a pharmacologically inert pill with the suggestion of pain relief may be mediated by an individual's prior experience with analgesic agents. With the repeated pairings of a small white pill and subsequent pain reduction (i.e., an aspirin taken for headache pain relief) pain reductions experienced from taking similar looking tablets could even become a conditioned response [25]. Fundamentally, the manipulation of expectations through verbal suggestion assumes a level of knowledge by an individual (i.e., what the suggestion means), and learning processes may be involved in acquiring this knowledge. Thus, within an expectancy paradigm in which participants are delivered suggestive instructions regarding particular outcomes, learning processes may play an important role in the generation of expectations.

2.4.3. Cognitive, behavioural, and emotional changes

The administration of a placebo treatment with the suggestion of benefit may generate changes in cognitions, behaviours, and emotional states, which can then influence outcomes [74]. For example, changes in cognitive processes, such as perceptual processing and attention, may influence symptom reporting [101]. With the expectation of reduced symptomatology, as generated by placebo suggestion, individuals may differentially attend to signs of improvement or ignore symptoms [102-105] which then results in the reporting of fewer symptoms.

Expectations of benefit may also generate changes in behaviour, which can then affect outcomes [74]. For example, placebo responses seen in surgery may reflect better adherence to medicinal and rehabilitation regimes [106] which then improve outcomes. Placebo-induced changes in depression may be mediated by increases in activity or social interactions [29, 74], which can be what ultimately generates the reductions in symptomology.

Equally, placebo-induced changes in emotions may mediate some placebo responses [107]. For example, the administration of a placebo treatment can reduce stress or anxiety because the patient or participant expects to experience benefit [74]. Anxiety and stress generate physiological processes, which can produce symptoms [108, 109]. By reducing stress and anxiety, the physiological symptoms associated with these responses may be reduced, and as a consequence individuals experience and report improvements in their conditions. Affective responses of this kind are often thought to play an important role in placebo analgesic responses [110-113].
2.4.4. Neurobiological mechanisms

It has been suggested that placebos can activate situation-specific neurobiological pathways on an as-needed basis [24, 45, 114]. That is, depending on whether the individual is experiencing pain, a stress response, or an allergic reaction (for example), placebo expectancy can stimulate appropriate endogenous homeostatic processes, and it is this homeostatic response that generates therapeutic benefit [25, 40, 115]. While specific networks have been identified as mechanisms of action (e.g., the activation of dopaminergic and opioidergic systems [116, 117]), in-depth discussion of these specific mechanisms is outside the scope of this thesis (see [24] for a review). However, across this situation-specific activity is a general pathway of action which is conceptually useful in interpreting findings and guiding research.

This general pathway posits that expectancy-induced placebo effects arise from an area of the brain called the pre-frontal cortex (PFC) [29], which is responsible for executive decision making [118] and the regulation of emotions, thoughts, attention, and behaviour, including adaptive and flexible responses to environmental demands [119]. When a placebo manipulation generates expectations, the PFC may then activate the appropriate top-down regulatory processes [114] as it would in coordinating any psychobiological response, such as activating a physiological stress response (e.g., cortisol release, increases in heart rate), once an environmental stimulus has been perceived as stressful [120]. This top-down regulatory pathway offers a useful general mechanism of expectancy-induced placebo effects.

In summary, there are a number of overlapping mechanisms by which expectancy-based placebo paradigms can exert effects on outcomes. Response expectancies, learning processes, cognitive, behavioural, or emotional changes, and top-down neurobiological pathways, may all contribute to the alleviation of symptoms when an individual expects to experience benefit. As described earlier, verbal suggestion is one way of generating expectancy-based placebo effects, and this is the paradigm employed in the current programme of doctoral research. Placebo suggestion has been shown to exert beneficial effects in a range of conditions and settings; however, there are limitations to this literature, as described next.
2.5. The placebo suggestion literature

Suggestive placebo protocols are those in which a placebo treatment is administered with the suggestion that it will have a particular effect, such as symptom alleviation or other therapeutic benefit. Thus, this paradigm resembles clinical encounters, in which a health practitioner identifies symptoms and prescribes a treatment regime with an explanation of what the patient can expect. Placebo effects generated by suggestive instruction have been demonstrated in experimental settings across both patient and healthy samples – a brief overview of which is provided next in light of the design and purpose of the current research programme.

2.5.1. Suggestive placebo protocols in patient and healthy samples

The power of placebo suggestion has been observed in clinical trials for a range of ailments [29, 121], and experimentally demonstrated in conditions such as Parkinson’s disease [122-125] irritable bowel syndrome (IBS) [46, 126-128], hypertension [129, 130] and asthma [131-136]. Such findings lend weight to the purported clinical validity of the placebo effect; however, while these studies have yielded important data regarding placebo effects in specific illnesses, there are limitations to this research approach, such as ethical issues and the introduction of heterogeneity into experimental investigations.

For example, in conducting a placebo study (i.e., rather than observing placebo responses in clinical trials), deception is often needed, otherwise the potential efficacy of the placebo can be adversely affected [137]. However, there are ethical issues inherent in deceiving patient samples, especially those who are psychologically or physically vulnerable. There is a risk of suicide, for instance, in those with major depressive disorder [138], and it may be unethical to deceive such patients about treatment. Other patient samples have life threatening illnesses (such as cancer), for which aggressive pharmacological approaches are vitally important. Relatedly, an intervention that has not yet been tested in a particular form or in a particular health setting should first be tested in a healthy sample to determine its efficacy.

Less vulnerable patient populations, such as those suffering from IBS or asthma, confer less of an ethical challenge in this regard; however, findings from studies using specific patient populations
are not necessarily transferable to other conditions. Further, the use of these samples can introduce potentially confounding variables. For example, disease factors (e.g., severity or length of illness) create heterogeneity within the sample and introduce variability not due to the experimental manipulations. Other, less quantifiable factors such as the psychological contributions to the symptoms and an individual’s subjective experience of the illness, may introduce further variation.

While the use of a healthy sample reduces the possible clinical applicability of findings, it is less ethically challenging and enables the implementation of rigorous protocols which may yield causal inferences from the results. In healthy volunteers, the power of suggestive instruction can be investigated by administering a placebo treatment with the suggestion of a certain outcome. Research in this area has demonstrated that different instructions can increase and decrease heart rate [93], blood pressure [139], and other autonomic nervous system parameters [140], as well as influence motor function [141, 142], individual muscle groups [143] and enhance sports performance [144-146].

In closer approximation of a clinical sample, placebo effects can be investigated in healthy volunteers by first administering noxious stimuli to induce symptoms, then administering a placebo treatment with the suggestion of symptom alleviation. This paradigm has been thoroughly utilised in the context of experimentally-induced pain [25, 121, 147, 148], which has yielded the bulk of the evidence for suggestion-induced placebo effects [121]. While this paradigm has produced important information about the placebo phenomenon, the focus on pain also represents a limitation of the extant placebo literature.

2.5.2. The prolific placebo analgesia paradigm: a limitation of the literature

The placebo analgesia paradigm is easily the most prolific and possibly the most convincing area of placebo research [149-153]. Since the 1970s, verbally-induced placebo analgesic effects have been repeatedly demonstrated by way of a number of different experimental protocols [25, 86, 91, 96]. As a result, this paradigm has fairly definitively demonstrated that the placebo effect is real, and it can be powerful.

The focus on (and success of) placebo analgesic effects in the literature likely reflects a number of factors, including the incremental nature of research and the tendency for researchers to work within a particular field of expertise, especially a successful one. Additionally, pain is easy to
manipulate experimentally and while it is subjective, there are techniques and tools that can be used to objectively track the activation of pain systems [154, 155].

However, while pain is common, it is also complex [156, 157]. As such, there may be factors unique to the regulation of pain, such as the engagement of opioid networks, which mean placebo analgesic responses are distinct from other placebo responses. Additionally, the paradigms in which painful stimuli are administered often involve complicated equipment and procedures which may further reduce the generalisability of findings. That is, such procedures may create a fairly unique environment in which a participant is responding and thus the findings may not apply to other contexts. Further, findings which arise from such an environment cannot be taken as representative of the modal clinical setting in which a practitioner delivers a simple prescription to the patient in the absence of complicated equipment and protocols.

Finally, while pain is a widespread and chronic ailment for which alternatives to pharmacological treatment are needed, there are a number of other pervasive and debilitating problems which also have iatrogenic risks, and for which standard medicinal approaches may not be uniformly suitable (see Chapter 1.1). To advance scientific research and to maximise the clinical utility of the placebo phenomenon, more research is needed to investigate placebo effects in other such contexts.

Thus, the first research question investigates the power of placebo suggestion beyond the context of pain. The three empirical works presented next detail a series of experimental studies investigating placebo effects in non-pain contexts, each approximating a pervasive and burdensome condition which enhances the possible clinical utility of placebo treatments: (1) physiological recovery from psychosocial stress, (2) inflammatory skin reactions; and (3) stress, anxiety, and depressive symptoms arising from the demands of daily life. Note that all studies included systematic personality assessment as part of the design; however, the question of who is responsive to placebo manipulations in each of these contexts will be addressed later in the thesis (Chapter 4).
3. THE PLACEBO EFFECT OUTSIDE THE PAIN PARADIGM

The evidence for placebo effects in non-pain settings is comparatively modest [50]; however, with the bulk of research being conducted in pain paradigms, this could indicate that, rather than placebos having limited utility beyond pain contexts, more research is needed to properly investigate placebo effects in other areas. For example, a meta-analytic review which concluded that placebo effects were limited to subjective outcomes and the alleviation of pain [49] was likely influenced by the fact that only pain, of the 40 conditions reviewed, had a large enough pooled sample to properly investigate the size of effects [53].

The criticism that placebo effects may only be valid for self-reported outcomes is related to this same issue, wherein self-reported pain is the outcome measure for the majority of studies. Regardless of the reason, there is more evidence for placebo effects when subjective outcomes are used [47, 49, 50, 53, 136, 158], a pattern that means findings could be attributable to reporting biases [50] rather than genuine psychobiological changes. The evidence for placebo modification of objective outcomes in clinical trials has been described as 'scant' [70] and the reliance on self-reported measures could be considered another limitation of the literature [136].

The autonomic nervous system (ANS) is involved in many physiological functions and can be used to index the human stress response [120]. As such, ANS activity represents a non-pain, objectively measurable outcome variable, which can be manipulated experimentally by the induction of acute physical and psychological stress tasks. Placebo-induced changes in ANS activity have been demonstrated in the context of physical stressors (painful challenges) [110], and there is some evidence that placebo suggestion can influence ANS parameters via the top-down regulatory systems described earlier [136]. However, results have not been consistent [136, 153], implying that more research is needed to investigate the suggestion-induced modulation of ANS function.

The following paper presents findings from the first experimental study in the doctoral research programme. This study investigated the power of placebo suggestion to enhance physiological stress recovery from a psychosocial stressor, thus addressing the need for more research in non-pain contexts as well as the use of physiological (objective) outcome measures.
3.1. The placebo effect in the context of physiological recovery from psychosocial stress


3.1.1. Abstract

**Objective**: To investigate placebo effects on heart rate (HR) and heart rate variability (HRV) in recovery from a psychosocial stressor. **Methods**: A healthy sample underwent two mental arithmetic stress tests in one experimental session. After undergoing the baseline test, participants were randomized into control or placebo groups. Prior to the second stress test, the placebo group received an intranasal dose of ‘serotonin’ (placebo) with the suggestion that it would enhance recovery. HR and HRV were assessed throughout procedures. **Results**: There was an increase in vagally-mediated HRV in the placebo group. The change in HR did not differ between groups. **Conclusions**: Placebo suggestion can enhance autonomic recovery after psychosocial stress. Findings are consistent with the notion of top-down mechanisms of placebo effects, but further research would need to specifically examine the role of top-down regulatory pathways as possible mediators of placebo-induced changes in autonomic function.
3.1.2 Introduction

Once dismissed as a nuisance factor in clinical trials, the placebo effect is now acknowledged as a genuine psychobiological phenomenon [29]. Placebo protocols can stimulate endogenous neurobiological systems [40-42], generate psychophysiological responses [43-45], and even change the brain [147]. Responding to placebo treatments may represent a sort of endogenous healthcare system [29].

There are a number of ways of generating placebo effects [29, 121]. Placebo-induced expectations, in which the suggestion of symptom improvement or therapeutic benefit is delivered with placebo treatment, has been investigated most extensively in experimental pain [25, 147, 148]. Consequently, much is known about the capabilities and mechanisms of placebo effects in this area, but for other areas such autonomic nervous system (ANS) activity there is a relative dearth of research [152, 153]. While there are established links between the ANS and pain regulation networks [159], the specific modulation of ANS function by placebo suggestion represents a different question.

Heart rate variability (HRV), the beat-to-beat variation in heart rate, is a measure of the ANS that indexes cardiac regulation [160]. HRV is believed to represent the fluctuations in autonomic inputs to the heart, with the parasympathetic and sympathetic systems working in dynamic equilibrium to regulate an organism’s reaction to and recovery from stress [120]. The neurovisceral integration model describes a regulatory network with top down pathways between the prefrontal cortex (PFC) and the ANS, and HRV is thought to measure the PFC regulation of vagal activity [120].

In a similar manner, expectation-induced placebo effects are also thought to arise from top-down regulatory pathways that originate in the PFC [40, 115]. Suggestions of benefit are thought to generate cognitive expectations, which then stimulate endogenous homeostatic processes [25]. Considerations of this kind suggest that HRV might be a suitable index of ANS activity in response to a suggestive placebo manipulation.

Prior work has found HRV metrics to be somewhat unresponsive to placebo suggestion; however, HRV has typically been assessed as a potential mediator of primary outcomes measures rather than being the focus of the manipulation [139, 140] [161]. Given HRV’s role in regulating an organism’s response to stress [120], it would appear that attempts to modulate HRV would be best conducted in the context of stress. One study has shown that placebo suggestion can influence HRV parameters after a painful stressor [110]. However, given the established interplay between pain and
ANS networks [159], the use of a pain task to generate a stress response may be problematic, in that data may not necessarily translate into non-pain paradigms, or to psychological stress.

In experimental settings, the effects of psychological stress can be investigated with the use of psychosocial stressors such as noxious social evaluative tasks, which can generate a physiological stress response [162]. Further, perhaps the most validated HRV measures are those indexing the vagally-mediated return to homeostasis in recovery from a stressor [160, 163]. Thus, attempts to influence HRV specifically with a placebo protocol but without the confounds associated with pain processes, may be best accomplished with the use of a psychosocial stress task and the suggestion of enhanced recovery from the stressor.

The current report investigated whether a suggestion based placebo protocol could enhance recovery from experimentally induced psychosocial stress. An intranasal spray of ‘serotonin’ (the placebo) was administered with the suggestion that it would enhance recovery from a mental arithmetic stress test. Heart rate (HR) and HRV were measured during baseline and post manipulation phases. A control group underwent the same procedures except they did not receive the intranasal spray or the accompanying verbal suggestion. It was hypothesized that those in the placebo group would have an increase in HRV and a reduction in HR in the recovery period after the second stress test; relative to the first stress test and the control group.

3.1.3. Methods

Note, this study is part of a larger investigation into the placebo personality [164].

Participants

A sample of 63 volunteers (21 males and 42 females) was recruited via notices posted on university intranets, social media sites, and the distribution of flyers. No course credit was offered for participation. To be eligible, participants had to be able to read and write English, have no chronic medical or psychological conditions, and, if female, not be pregnant. Those eligible to take part were invited to participate and were sent consent forms before being scheduled for one 75-minute laboratory session. Of the 152 who initially expressed interest in the study, 91 (60%) returned the screening questionnaire and 75 of them (82%) were eligible with 17 excluded based on the criteria described above. Of the remaining 75, 11 either did not respond to the invitation or were unable to be scheduled for a laboratory
session. A total of 64 participants completed the experimental session, but one male participant had to be excluded upon completion as debriefing indicated he was not blind to the study purpose.

**Design, randomization and blinding**

This was a randomized controlled experiment. Participants were block-randomized into placebo or control conditions by blind selection from an envelope. The researcher carried out randomization procedures after they had delivered the introductory overview to the participant and left the lab (Figure 3.1). The research assistant (RA) remained in the lab and was not privy to the randomization process. The approach avoided the possibility of knowledge regarding group allocation affecting interactions between the participant, the RA, and the researcher during any Phase I procedures. The researcher delivered the placebo manipulation in Phase II, which enabled the RA to remain blind to group, and thus neutrally administer both stress tests. Participants were told the purpose of the study was to investigate the relationship between serotonin, stress reactivity and stress recovery (deceptive cover story).

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Introduction</th>
<th>Base 1 (5mins)</th>
<th>Stress Test 1 (5 mins)</th>
<th>Recover 1 (5 mins)</th>
<th>Break (5mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II</td>
<td>Base 2 (5 mins)</td>
<td>Video (~2.5 mins)</td>
<td>Stress Test 2 (5 mins)</td>
<td>Recover 2 (5 mins)</td>
<td>End</td>
</tr>
</tbody>
</table>

*Figure 3.1. Experimental protocol for Phase I and Phase II with shaded boxes indicating tasks carried out by the researcher (all others administered by the RA).*

**Procedures**

The RA carried out all Phase 1 procedures, starting with the baseline questionnaire (see measures), and a baseline ‘resting’ (seated) measure of HR and HRV (Base 1). The RA then administered the first stress test, a 5-minute mental arithmetic test adapted from a previous study [165]. Participants were told this was a ‘mental arithmetic IQ test’ and were asked sequentially to subtract a number (163) from a starting number (8500) as quickly as possible. Participants could not progress until they gave the correct answer. If they paused, they were prompted to carry out the task as quickly as possible. After
the stress test a 5-minute recovery period commenced (Recover 1). All participants underwent the same procedures for Phase I.

Phase II commenced with another baseline HR and HRV reading (Base 2). The RA then left the lab and was replaced by the researcher who remained in the lab for the duration of Phase II. Participants were then told whether they were in the ‘serotonin’ (placebo) group or the ‘comparison’ (control) group by the researcher and shown a brief video in which information regarding procedures was delivered by a credible source (an Associate Professor in the Medical School).

For those in the control group the emphasis of the video was on how important control groups were in experimental trials. Those in the placebo group were told that they would receive an intranasal dose of serotonin just before and just after the second stress test and this would enhance their recovery from the stress test. Consistent with the aim to utilise an explicit suggestion protocol, detailed information was provided about the stress response, how HRV was a measure of this, indexing autonomic regulation and sympathetic and parasympathetic activity, and that this would be measured by the heart rate monitor they were wearing. Serotonin was described as a neurotransmitter that plays a key role in stress recovery and its administration via the intranasal spray would reduce heart rate and stress, thus enhancing recovery from the stressor.

After this video, the researcher explained the administration and re-iterated its effects before administering one spray of the ‘serotonin’ (5% sterile saline solution) in each nostril. The control group were advised that they would undergo a second stress test. The control group did not receive an intranasal spray to avoid the possibility of this treatment ritual affecting responses [166]. The RA then re-entered the room and administered the second stress test. Participants were not advised of the nature of this test until it commenced. The second stress test was the same as the first, with the exception of the starting number (8600) the subtracting number (177) and the presence of the researcher (behind a screen), which was designed to counteract habituation by elevating the stress of the second test without deviating too much from Phase I procedures. Immediately after the stress test the RA left the room and placebo group participants received a top-up dose of ‘serotonin’ (same procedure) and were told this would ‘enhance their recovery during the five minute recovery period’ (the control group again received nothing), before all participants commenced the second 5-minute recovery period (Recover 2). Finally, participants were given a $20 voucher and thanked for their time.
3.1.4. Measures

**Self-report measures**

Demographics and self-reported health behaviours were assessed as potential confounds via a one page questionnaire (Table 3.1).

**Physiological measures**

HR and HRV were measured continuously with the non-invasive RS800 Polar HRV wristwatch and chest band [167, 168]. HR provides an indication of physiological arousal. HRV describes the beat-to-beat variations in HR, with lower HRV indicating a poorer regulatory response [169]. Vagal activity, which is primarily involved in returning the system to homeostasis, can be indexed by both time and frequency domain parameters [160, 170]. Two metrics were employed: (1) high frequency spectral power HRV, a frequency domain measure which represents primarily parasympathetic (vagal) activity; and (2) root mean square of successive differences (rMSSD), a time domain measure which indexes parasympathetic neural regulation of the heart [163]. HRV artefact correction was carried out in Kubois HRV 2.0 (Biosignal Analysis and Medical Imaging Group, Kuopio, FINLAND), which has a sampling rate of 1000 Hertz [171]. HRV values were positively skewed and were log transformed before analysis. The measures used in analyses were log high frequency ms² auto regression spectrum (HF), log rMSSD (rMSSD), and mean heart rate in beats per minute (HR).

3.1.5. Statistical Analysis

Between-group analyses were carried out to ensure there were no baseline differences in demographics or outcome variables. Chi-squared analyses were used for categorical variables and independent t-tests were used for continuous variables. Repeated measures ANOVAs were carried out to test placebo effects on the three outcome measures (HF, rMSSD, and HR). HR/HRV data from five participants was not available due to equipment issues. Several individual data points were not available for various HR and HRV variables and were treated as missing data. After log transformation, any remaining extreme outliers were removed [172, 173]. Two participants were excluded prior to hypothesis testing as they were unaffected by the stress test.
3.1.6. Results

Study Characteristics

The sample mean age was 21 years ($M = 20.67$, $SD = 2.55$, range 18-30), with 42 (68%) females and 20 (32%) males. Half the sample (50%) were Caucasian, 37% Asian/Indian and 13% ‘other’ ethnicities.

Grouped into Caucasian / Non-Caucasian ethnicities, the sample consisted of 50% in each group.

Table 3.1.
Between group differences in demographics, health behaviours, session time, and outcome variables pre and post manipulation; with means, standard deviations, degrees of freedom, test statistics, significance values and effect sizes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control $n = 31$</th>
<th>Placebo $n = 29$</th>
<th>Chi</th>
<th>df</th>
<th>p</th>
<th>$\phi$</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Female</td>
<td>21/31 (68%)</td>
<td>20/29 (69%)</td>
<td>.01</td>
<td>1</td>
<td>.57</td>
<td>.002</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>16/31 (52%)</td>
<td>14/29 (48%)</td>
<td>.07</td>
<td>1</td>
<td>.50</td>
<td>.004</td>
</tr>
<tr>
<td>Age</td>
<td>20.84 (2.62)</td>
<td>20.48 (2.50)</td>
<td>.54</td>
<td>58</td>
<td>.59</td>
<td>.14</td>
</tr>
<tr>
<td>BMI</td>
<td>22.42 (2.90)</td>
<td>22.08 (3.16)</td>
<td>.44</td>
<td>58</td>
<td>.66</td>
<td>.11</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>2.23 (1.26)</td>
<td>2.28 (1.13)</td>
<td>-1.6</td>
<td>58</td>
<td>.07</td>
<td>-.04</td>
</tr>
<tr>
<td>Caffeine intake</td>
<td>3.32 (1.01)</td>
<td>2.93 (1.19)</td>
<td>1.4</td>
<td>58</td>
<td>.18</td>
<td>.36</td>
</tr>
<tr>
<td>Activity Level</td>
<td>4.35 (1.17)</td>
<td>4.17 (1.42)</td>
<td>.55</td>
<td>58</td>
<td>.59</td>
<td>.14</td>
</tr>
<tr>
<td>Session time (24hour)</td>
<td>11.25 (2.14)</td>
<td>12.50 (2.37)</td>
<td>-2.15</td>
<td>58</td>
<td>.04</td>
<td>-.56</td>
</tr>
<tr>
<td>HR Base 1</td>
<td>83.04 (16.12)</td>
<td>84.52 (17.73)</td>
<td>-.32</td>
<td>52</td>
<td>.75</td>
<td>-.09</td>
</tr>
<tr>
<td>HR Stress 1</td>
<td>87.12 (10.40)</td>
<td>89.15 (17.36)</td>
<td>-1.17</td>
<td>53</td>
<td>.25</td>
<td>-.15</td>
</tr>
<tr>
<td>HR Recover 1</td>
<td>77.09 (10.18)</td>
<td>80.12 (12.96)</td>
<td>-0.97</td>
<td>53</td>
<td>.34</td>
<td>-.27</td>
</tr>
<tr>
<td>HF HRV Base 1</td>
<td>6.22 (1.35)</td>
<td>5.80 (1.93)</td>
<td>1.28</td>
<td>49</td>
<td>.21</td>
<td>.37</td>
</tr>
<tr>
<td>HF HRV Stress 1</td>
<td>6.20 (.94)</td>
<td>5.89 (1.14)</td>
<td>1.09</td>
<td>53</td>
<td>.28</td>
<td>.30</td>
</tr>
<tr>
<td>HF HRV Recover 1</td>
<td>6.68 (1.31)</td>
<td>6.29 (1.93)</td>
<td>1.25</td>
<td>53</td>
<td>.22</td>
<td>.35</td>
</tr>
<tr>
<td>rMSSD Base 1</td>
<td>3.70 (.63)</td>
<td>3.42 (.51)</td>
<td>1.79</td>
<td>50</td>
<td>.08</td>
<td>.55</td>
</tr>
<tr>
<td>rMSSD Stress 1</td>
<td>3.66 (.46)</td>
<td>3.49 (.59)</td>
<td>1.17</td>
<td>53</td>
<td>.25</td>
<td>.33</td>
</tr>
<tr>
<td>rMSSD Recover 1</td>
<td>3.81 (.55)</td>
<td>3.68 (.49)</td>
<td>.92</td>
<td>53</td>
<td>.36</td>
<td>.25</td>
</tr>
<tr>
<td>HR Base 2</td>
<td>75.50 (10.18)</td>
<td>79.40 (13.30)</td>
<td>-1.31</td>
<td>52</td>
<td>.20</td>
<td>-.34</td>
</tr>
<tr>
<td>HR Stress 2</td>
<td>83.47 (10.89)</td>
<td>85.49 (12.93)</td>
<td>-.73</td>
<td>52</td>
<td>.47</td>
<td>-.17</td>
</tr>
<tr>
<td>HR Recover 2</td>
<td>75.13 (9.40)</td>
<td>75.55 (10.31)</td>
<td>-.16</td>
<td>52</td>
<td>.88</td>
<td>-.04</td>
</tr>
<tr>
<td>HF HRV Base 2</td>
<td>6.64 (1.27)</td>
<td>6.15 (1.93)</td>
<td>1.55</td>
<td>50</td>
<td>.13</td>
<td>.44</td>
</tr>
<tr>
<td>HF HRV Stress 2</td>
<td>6.55 (1.13)</td>
<td>6.30 (1.99)</td>
<td>.84</td>
<td>51</td>
<td>.41</td>
<td>.24</td>
</tr>
<tr>
<td>HF HRV Recover 2</td>
<td>6.65 (1.12)</td>
<td>6.81 (1.83)</td>
<td>-.60</td>
<td>52</td>
<td>.55</td>
<td>-.17</td>
</tr>
<tr>
<td>rMSSD Base 2</td>
<td>3.89 (.56)</td>
<td>3.64 (.43)</td>
<td>1.80</td>
<td>52</td>
<td>.08</td>
<td>.51</td>
</tr>
<tr>
<td>rMSSD Stress 2</td>
<td>3.81 (.52)</td>
<td>3.68 (.49)</td>
<td>.95</td>
<td>52</td>
<td>.35</td>
<td>.33</td>
</tr>
<tr>
<td>rMSSD Recover 2</td>
<td>3.89 (.51)</td>
<td>3.95 (1.41)</td>
<td>-.48</td>
<td>52</td>
<td>.63</td>
<td>-.13</td>
</tr>
</tbody>
</table>
Between-group analyses revealed there were no differences in demographics, health behaviours, and pre-manipulation outcome measures; however, there was a difference in time of experimental session (Table 3.1). That is, the time of day that participants underwent experimental procedures was different between the groups, with those in the placebo group, on average, having a slightly later appointment time (Table 3.1). Given the potential impact of circadian rhythms on physiological measures [174], ‘time of session’ was added as a covariate in analyses. There was no difference between the groups in respiration rates during procedures [175], calculated by multiplying peak HF by 60. It has been noted that gender can affect responses to stress [176]; however, there were no sex differences in the outcome measures so it was not added as a covariate.

**Placebo effects**

The suggestive manipulation sought to increase HRV and decrease HR in the placebo group after the second stress test. Three 2 (Group) x 2 (Time) repeated measures ANOVAs were carried out to investigate differences in recovery across the two stress tests (Recover 1 to Recover 2). There was an interaction between Group and Time on both HRV metrics. The placebo group had a greater increase in HF HRV (Wilks λ = .90, $F(1,51) = 5.81$, $p = .02$, $\eta^2 = .10$, Figure 3.2), than controls, with a similar pattern observed for rMSSD (Wilks λ = .91, $F(1,51) = 5.03$, $p = .03$, $\eta^2 = .09$, Table 3.1). There was no Group by Time interactive effect on HR (Wilks λ = .95, $F(1,51) = 2.65$, $p = .11$, $\eta^2 = .05$, Figure 3.3).

![Figure 3.2. Log high frequency ms$^2$ auto regression spectrum HRV by Group from Recover 1 to Recover 2 (error bars are standard error of the mean) controlling for time of day.](image_url)
3.1.7. Discussion

To date, this is the first study to show the placebo modulation of HRV in the context of psychosocial stress. The increases in vagally-mediated HRV after the placebo manipulation indicates that the suggestive manipulation enhanced physiological recovery from the stressor [169]. Instructions for the vagal system are thought to originate from the PFC [120], so the increased vagal activity after the verbal manipulation of expectation suggests top-down regulatory activity may have occurred. As noted, the neurovisceral integration model maps out top-down pathways between the PFC cortex and the ANS [120] and top-down regulatory pathways originating from the PFC have also been identified in expectation-induced placebo effects [40, 115]. Taken together, these findings provide at least broad support for the purported top-down pathways thought to mediate some expectation-based placebo effects [40], and offers the possibility that these mechanisms may apply in the context of autonomic function. Further research would be needed to test this notion specifically.

Applied clinically, the increase in heart rate variability after the placebo treatment represents a potentially beneficial health outcome. Low HRV has been reported as a predictor of all-cause mortality, coronary events, cardiovascular disease, slower recovery following myocardial infarction, immune dysfunction and inflammation [160, 177-180]. Further, prolonged or chronic activation of the stress system can lead to health problems [109, 181]. Thus, a placebo-induced return to homeostasis
after noxious events and stressors could be a pathway by which placebo treatments might exert beneficial effects on health.

Heart rate was not affected by the manipulation, which is consistent with some research [139, 140], but contrary to others [93, 161]. Heart rate is a function of a complex interplay between the branches of the ANS and thus fluctuations can be difficult to interpret [159, 182]. Further, the drop in heart rate from the first to the second stress tests across both groups may suggest a relaxation response or habituation to the protocol. This general reduction in arousal may have made it harder to detect manipulation-specific differences in heart rate. Finally, changes in heart rate may reflect the performance nature of mental arithmetic task and may have represented a challenge for some, rather than an unpleasant stressor. Overall, the multiplicity and interdependencies among the determinants of heart rate may make it difficult to systematically modify.

Several limitations of this study need to be acknowledged. A student sample was used, which can affect generalizability; however, it does offer a much smaller age range which is desirable given age related changes in heart rate variability. Although suited to the sample, the external validity of an experimental mental arithmetic stress test is limited. The baseline difference in the time of experimental session indicates a partial failure of randomization, which cannot be explained. These limitations noted, this study offers several novel contributions to placebo research. The use of an intranasal dose of ‘serotonin’ to enhance recovery from a psychosocial stress test has not been demonstrated in prior work. It also appears no other study has attempted direct modulation of HRV within a psychosocial stress recovery paradigm.

In conclusion, the current study demonstrated increased HRV after the administration of placebo treatment. Findings are consistent with notion of top-down mechanisms of placebo effects, but further research would need specifically to examine the role of top-down regulatory pathways as possible mediators of placebo-induced changes in autonomic function. Equally, whether short-term, laboratory-induced increases in vagal activity represent a clinical benefit is not yet known but, given the established relationship between psychological stress and health outcomes, it would be worth further investigating the possible applications of placebo treatments to reduce stress. There is clinical utility in a cheap, portable, non-invasive treatment that can potentially enhance recovery from stress.
3.2. Interim commentary: from psychosocial stress to inflammatory skin reactions

The preceding study demonstrated that placebo suggestion can enhance physiological stress recovery, which addresses two limitations within the extant placebo literature: the reliance on pain paradigms and the predominance of self-reported outcome measures. These findings contribute to a relatively small body of work demonstrating that placebo suggestion can exert effects on human physiological function, and findings indicate that placebo treatments might be useful in alleviating psychological stress. However, while short-term stress induced by a mental arithmetic test in a laboratory may be suited to the sample and the measures employed, it is not easily transferable to a general population suffering from stressful life events.

Further, while scientifically useful, these findings cannot necessarily be generalised beyond this paradigm, and there are other notable gaps in the placebo literature. For example, placebo effects in immune functioning have been demonstrated via classical conditioning protocols [45, 183], but to date there is virtually no evidence that suggestive placebo manipulations can influence immune parameters [45]. While the lack of evidence may imply that immune function is not modifiable by verbal suggestion [123], it may also be that only certain aspects of immune function are suited to such manipulations [184].

That is, with expectations conceptualised as cognitively accessible, conscious processes [29, 53], an immune parameter that can be consciously perceived may be needed for a suggestive placebo paradigm to be effective [27]. If an individual’s expectations are to activate top-down regulatory processes, as described earlier (Chapter 2.4.4), then it follows that they need to be able to perceive and consciously, subjectively experience the processes that are being regulated. Most immune system activity takes place outside of conscious awareness, but some aspects of immune functioning have effects that are cognitively perceptible.

Inflammatory skin reactions are one notable example. The skin is a unique organ because it can be seen and felt [185]. Further, inflammatory skin reactions can be experimentally induced with the administration of histamine directly on the skin able to approximate skin conditions like urticaria [186]. Skin reactions thus provide a context in which the regulation of skin reactivity by top-down pathways can be examined [187]. Placebos have been shown to decrease itch in clinical trials of chronic skin conditions [188] and a protocol combining suggestion and learning protocols has
demonstrated effects on itch [189]; however, placebo effects in inflammatory skin reactions by a suggestion-only placebo protocol has not yet been demonstrated.

The second experimental study presented in this thesis investigated the modulation of short-term inflammatory skin reactions by placebo suggestion. The ability to influence skin reactions by treatments with no pharmacological properties (and thus less risk of iatrogenic harm) may have clinical utility in the treatment of chronic skin conditions. In the context of placebo research, this investigation extends the literature beyond the pain paradigm into a promising domain in which suggestion-induced placebo effects on immune parameters can be examined.
3.3. The placebo effect in the context of inflammatory skin reactions


3.3.1. Abstract

**Purpose:** To investigate suggestion-induced placebo effects in inflammatory skin reactions. **Methods:** A healthy sample of volunteers (N=48) attended two laboratory sessions. In each, a local short term inflammatory skin reaction was induced with histamine. Participants were told that one session was a control session and the other was a treatment session in which an antihistamine cream would be applied to the arm to reduce the size of the weal and the experience of itch. Inert aqueous cream was applied in both sessions. Participants were randomly allocated to undergo either the control or the treatment session first. **Results:** The placebo manipulation successfully reduced self-reported itch from the control to the placebo treatment session, but no placebo effect was demonstrated in weal size. Order effects were observed such that only those who underwent control procedures first had a smaller weal in the placebo treatment session as compared to the control session. The same order effect was seen for reported itch at one minute post histamine administration, but this disappeared at the three and five minute measures. **Conclusion:** Findings suggest that explicit verbal suggestion can reduce the experience of itch. In addition to conscious awareness, a concrete representation of the suggested changes gained from prior experience to the stimulus may be an important component of placebo effects on inflammatory skin reactions.
3.3.2. Introduction

The relative importance of psychological factors in skin conditions such as urticaria continues to be debated [190], but there is empirical evidence to suggest that they can influence the experience of itch [191, 192] and contribute to idiopathic conditions such as chronic spontaneous urticaria [6]. The way an individual thinks and feels appears to impact the status of the skin; however, whether this ‘mind-body’ relationship can be harnessed to ameliorate the symptoms of skin conditions is less clear.

The placebo effect is an intriguing phenomenon in which individuals experience benefit from pharmacologically inert treatments [121]. Expectation, an established mechanism of some placebo effects, is when the patient or participant’s expectation of improvement generates real psychobiological changes [29]. Explicit suggestion of benefit is often used to induce expectations, such as providing verbal instructions that a treatment cream will reduce the experience of pain [27]. Placebo-induced expectations are thought to modulate internal homeostatic processes by activating top-down, neurobiological pathways [29, 114]. Thus, placebo research has been described as investigations into the ‘impact of expectations on brain-mind-body interactions’ [193 p.1922].

While psychological factors are known to influence the immune system [194], there is a paucity of evidence demonstrating that placebo expectancy can exert changes on immune parameters [45]. One possible reason for this is that certain placebo protocols may be more appropriate for the manipulation of certain outcomes. For example, those outcomes of which we are consciously aware (such as pain or motor function) can be influenced by suggestion, unlike those that not consciously detectable, such as hormone release [123]. Therefore, in order for a suggestive placebo protocol to be effective, a conscious awareness of the suggested changes may be needed [61]. Given the nature of the immune system, this type of awareness is often not possible; however, inflammatory skin reactions can be seen and felt [185], and may be an appropriate target for suggestive placebo protocols.

Only a few studies have attempted to influence inflammatory skin reactions by way of suggestive placebo protocols. One study aimed to reduce histamine induced skin reactions with verbal suggestion and the application of topical ‘anti-histamine’ (placebo) cream [161]. While the manipulation was not successful, the suggestion did not explicitly suggest a smaller weal size or a reduction in perceived itch, but instead a ‘dampened’ response to the histamine. Another study demonstrated a suggestion-induced increase in itchiness, but the suggestion of decreased itchiness was not successful [195]. A recent study demonstrated that while verbal suggestion alone did not
modulate itch, placebo effects were demonstrated when suggestion was coupled with a conditioning procedure [189].

While attempts to demonstrate placebo effects in this area have been more successful when conditioning protocols are employed [45], hypnosis (a form of suggestion) can influence immune parameters [196] cognitive-hypnotic protocols have been shown to modulate local inflammatory skin reactions [194, 197-199], and emotion and arousal mood states can affect hypersensitivity skin reactions [200, 201]. Reviews of placebo responses arising from the placebo-control arm of allergy treatment trials found placebo treatments can reduce skin symptoms [202, 203]. The possibility that local inflammatory skin reactions may be modifiable by suggestion alone remains worthy of investigation.

The aim of the current study was to investigate whether a histamine-induced inflammatory skin reaction could be modulated by a suggestive placebo protocol. Explicit suggestions of a reduced weal size and less itching were provided conjointly with a topical ‘anti-histamine’ (placebo) cream. It was hypothesised that when the application of the cream combined with the suggestion of a reduced reaction, participants would experience reduced itchiness and a smaller weal size.

3.3.3. Materials and Methods

Design, randomization and blinding

This was a randomized, cross-over, experimental study using a deceptive placebo protocol. Participants were told that the study was investigating the relationship between personality and allergic responses, and each participant attended two laboratory sessions. Local type-I hypersensitivity-like skin reactions were induced on both arms in each session (histamine prick tests). Participants were told that one session was a control session, and the other a treatment session in which an anti-histamine treatment cream would be applied to reduce the skin reaction. In reality, an inert aqueous cream was applied to the arms in both sessions. Participants were randomized to undergo either the control session first (Group 1), or the treatment session first (Group 2) (Figure 3.4), and were informed of which session they were in (‘Session’) by receipt of an envelope at the start of each session. The research assistant (RA) performing the experiment was kept blind to Group and Session by providing information to the participants through video and written information in sealed envelopes.
Figure 3.4. Overview of study design

**Participants, recruitment and enrolment**

Ethical approval was granted by the University of Auckland Human Participant Ethics Committee. A healthy sample of 50 volunteers was recruited, primarily through the distribution of flyers and notices posted on the University intranet (Figure 3.5). No course credit was offered for participation. The sample mean age was 22 years (SD = 3.25), predominantly female (79%), with Caucasians the largest ethnic group (42%), followed by non-Indian Asians (33%), Indian (15%), ‘Other’ (6%) and Māori and Polynesian (4%). Inclusion criteria were English-speaking adults aged between 18 and 45. Exclusion criteria were recent anti-histamine or anti-inflammatory medication, pregnancy, cardiac, autoimmune, psychological, or dermatological conditions, life threatening allergies, injury to either arm, or chronic illness. Eligibility was determined by a screening questionnaire prior to enrolment.

Figure 3.5. Overview of the recruitment and enrolment process
**Procedure**

Prior to the first laboratory session, participants completed an online survey consisting of personality, demographic, and health behaviour measures. Participants were then scheduled for two, 30-minute laboratory sessions, which were a minimum of one day and a maximum of three days apart. The two sessions were carried out at the same time of day (± 1 hour) to avoid circadian fluctuations in physiological processes and mood affecting experimental procedures [201, 204]. Participants were asked to avoid food, caffeine, smoking, applying any cream to their forearms, and strenuous exercise, in the two hours prior to their sessions, and to avoid alcohol on the session days.

Both sessions started with a general overview of procedures. Participants were given an envelope explaining whether this was a control or a treatment session; then, to facilitate adaption to the laboratory context and help balance arousal between the sessions, participants listened to a 5-minute relaxation exercise which focused on mindful attention and calm and steady breathing. Participants completed a measure of negative mood (see Measures) before watching a ~2-minute information video, the content of which differed depending on the session. In the control session, participants were told the purpose of the session was to get an indication of their skin reactivity without treatment, and that an inert aqueous cream would be applied to their arms before the histamine was administered. In the treatment session, the video explained that an anti-histamine treatment cream would be applied to their arms before the histamine was administered and that the cream would work to counteract the effects of the histamine, reduce itchiness, and the size of the weal:

‘The cream works as anti-histamine and has been shown to be effective in reducing the effects of histamine and alleviating the symptoms. When applied to the skin, it reduces itching, and reduces the size of the weals (which are the red raised lumps).’

Participants were then provided with a one-page information sheet which re-iterated the information in the video (that the cream was either an inert moisturizer or that it was an anti-histamine cream which would reduce weal size and itchiness). Participants were then seated comfortably on a chair and asked to place their arms palm up and in a natural position on a large pillow sitting on their lap. Aqueous cream was applied to an eight centimetre area in the middle one-third of the anterior surface...
of the right, then the left forearm with a cotton bud, and left to dry for approximately two minutes. As noted, video and information sheets led participants to believe that the cream had either no effect (control session) or it had antihistamine effects (treatment session).

Approximately 2 minutes after application of the cream, histamine was administered. Three droplets of histamine (all 10mg/ml in 5% glycerol, physiological saline) were placed on the same section of arm that the cream had been applied. The drops were placed approximately two centimetres apart, avoiding veins, hair, or other blemishes where possible. The skin was then pricked through each histamine droplet with a 1mm prick lancet. The histamine droplets were left on the forearms for 40 seconds. The same part of the forearm was used for each participant across the two sessions. The histamine was always administered to the right arm first (irrespective of dominance), with care taken to ensure that the histamine was left on both arms for the same amount of time. At 1, 3, 5 and 7 minutes post-administration, self-reported itch was measured. The right and left arms were assessed separately, again with care taken to ensure that the timing between histamine administration and assessment of itch was the same for both arms. Procedures for each arm were the same, carried out at the same time, with an approximate 30-second lag between the right and the left arm.

Photographs of the skin reaction were taken at eight minutes post-histamine administration with a Canon EOS 600D camera (Canon Ltd., Tokyo, Japan) using a Canon EF 50 mm F1.8 II lens. A prior study using a similar method took weal measures at 6 and 10 minutes and found no difference between the two [161], so the mid-point was used for the current study. A calibration scale was placed on the forearms below the weal closest to the wrist before the photo was taken. Camera settings were as follows: manual mode, ISO 400, 1/30 s, F8.0, ‘standard’ picture style, ‘white fluorescent light’ white balance, and evaluative metering. Participants’ forearms were positioned at a standard distance from the lens by keeping the focus ring of the lens constant, and adjusting the distance between the lens and the forearms until the shot was in focus.

At the completion of their second session, participants were provided with a $20 petrol voucher and thanked for their time. Participants were debriefed after completion of data collection.

**Measures**

*Pre-experiment questionnaire*
Demographic and health information (age, sex, ethnicity, body mass index (BMI), allergies, and self-reported health) was gathered 1-2 weeks prior to the experimental sessions via an online survey. Personality constructs were also measured but these data will be reported elsewhere.

**Weal size**

Photographs of the weals were uploaded to *Image J* (*National Institutes of Health, USA*). In each session, the weals on each arm were measured via the calibration ruler captured in the photographs. Horizontal and vertical diameters for each weal were taken, which yielded a possible six measurements per arm, per session (a total of 24 values for each participant). For use in analysis, an average of the horizontal and vertical diameters was taken for each weal, then an average of the three weals was calculated for each arm (in each session). These measures provided an estimate of weal area, with a control session average weal size and a treatment session average weal size for each arm. The average weal size of the right and left arm were highly correlated ($r_s = .70$ and $ .79, p < .001$) so an average across both arms was used in analysis. Note, analyses were conducted with right and left arm separated as a precaution, but these yielded no differences in the results.

**Missing weal data**

In some cases the horizontal or vertical diameters could not be measured as weal boundaries could not be discerned. Given the histamine concentration was the same for each weal, and there were multiple measures, where one measure was missing an average was estimated from the other values. Because of the number of individual data points available, there were no instances where an average was not able to be imputed using the remaining data. Of 1152 data points (24 x 48 participants), 56 (5%) individual data points were missing. Of these, 24 (4%) were from the control session and 32 (6%) were from the treatment session. There was no difference in the number of missing weal data points between the control and treatment sessions ($\chi^2 = 1.31, p = .27$).

**Itch**

Participants’ self-reported itch was measured at 1, 3, 5 and 7 minutes post-histamine administration. Participants were asked to rate the itchiness on each forearm (separately) using an eight-point scale from $0 = \text{ ‘not at all’}$, to $7 = \text{ ‘extremely’}$. This rating was used as a primary outcome measure.
Negative Mood: Brief Mood Rating (BMR)[201]

Negative arousal mood states (e.g., tense, irritable, annoyed) have been related to weal size in prior work [201], so participants were asked at the start of each session to indicate how much this type of negative mood they were experiencing by placing marks on 100mm visual analogue scales: tense-relaxed, irritable-agreeable, nervous-calm, stressed-at ease, jittery-tranquil, and annoyed-patient. A negative mood score was created for both sessions, with the scale coded so that higher scores indicated greater negative mood. The scale had good internal consistency in both sessions (Cronbach’s $\alpha = .84$ to .89).

Table 3.2.
Results of baseline between group tests with test statistics, degrees of freedom, significance levels and effect sizes.

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>Group 1 (CX then TX) n = 24</th>
<th>Group 2 (TX then CX) n = 24</th>
<th>$\chi^2$</th>
<th>df</th>
<th>p</th>
<th>$\Phi$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% Female)</td>
<td>19(79%)</td>
<td>18(75%)</td>
<td>.12</td>
<td>1</td>
<td>.73</td>
<td>.02</td>
</tr>
<tr>
<td>Ethnicity (% European)</td>
<td>10(42%)</td>
<td>12(50%)</td>
<td>.34</td>
<td>1</td>
<td>.56</td>
<td>.05</td>
</tr>
<tr>
<td>Allergies (%)</td>
<td>5(21%)</td>
<td>11(46%)</td>
<td>3.34</td>
<td>1</td>
<td>.07</td>
<td>.48</td>
</tr>
<tr>
<td>Right handed (%)</td>
<td>22(92%)</td>
<td>23(96%)</td>
<td>.36</td>
<td>1</td>
<td>.55</td>
<td>.05</td>
</tr>
<tr>
<td>Age</td>
<td>21(2.49)</td>
<td>22(3.81)</td>
<td>-1.30</td>
<td>46</td>
<td>.20</td>
<td>-.32</td>
</tr>
<tr>
<td>BMI</td>
<td>21.47(2.94)</td>
<td>22.77(3.22)</td>
<td>-1.45</td>
<td>46</td>
<td>.20</td>
<td>-.43</td>
</tr>
<tr>
<td>Dr visits (last 12 mths)</td>
<td>2.46(3.39)</td>
<td>2.25(2.17)</td>
<td>.26</td>
<td>48</td>
<td>.80</td>
<td>.08</td>
</tr>
<tr>
<td>Session 1 neg mood</td>
<td>123.25(66.63)</td>
<td>115.50 (72.94)</td>
<td>.38</td>
<td>46</td>
<td>.70</td>
<td>.11</td>
</tr>
<tr>
<td>Session 2 neg mood</td>
<td>142.33(75.06)</td>
<td>145.54(90.24)</td>
<td>-.13</td>
<td>46</td>
<td>.89</td>
<td>-.04</td>
</tr>
</tbody>
</table>

3.3.4. Results

Preliminary analyses
Between-group tests were carried out to assess potential baseline group differences (Table 3.2). Analyses revealed there was a trend for a between-group difference in the incidence of allergies (Table 3.2); so as a cautionary measure, tests were run with allergies as a covariate. Because negative mood has been linked to weal size in prior work [201], a test assessing whether negative mood changed from the first to the second session (i.e., regardless of whether it was a control or treatment session), was carried out. There was an increase in negative mood from Session 1 ($M = 119.38$, $SD = 69.22$) to Session 2 ($M = 143.94$, $SD = 82.13$, $t(47) = -2.55$, $p = .01$). Consequently,
change in negative mood was added as a covariate to outcome analysis (reported below). Itch and weal data were coded so that each participant had itch scores for their control (CX) session, as well as their treatment (TX) session. This enabled an assessment of reduction from CX to TX across both groups. Note, because the right and left arm values were highly correlated ($r > .50$, $p < .001$) an average was used in analyses; however, as a precaution, separate right and left arm analyses were also run, but these yielded no differences to the results reported below.

**Placebo effects**

To concurrently test (1) for placebo effects, i.e., whether the placebo manipulation reduced skin reactivity from the control to the treatment session, (2) whether there was an effect of Group (i.e., the order in which participants underwent control or treatment procedures), and (3) whether allergies or changes in negative mood affected results; five 2 (Group) by 2 (Session) repeated measures ANCOVAs were carried with allergies and change in negative mood co-varied. Results are reported in Table 3.3.

Table 3.3.
*Results of repeated measures ANCOVAs testing for main effects of Session (placebo effects) and Group (order of session) while controlling for the presence of allergies (Allergies) and changes in negative mood (Negative Mood).*

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Group 1 M (SD)</th>
<th>Group 2 M (SD)</th>
<th>Main effects</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Session</td>
<td>Group</td>
</tr>
<tr>
<td>CX 1 min</td>
<td>3.77(1.71)</td>
<td>3.33(1.62)</td>
<td>F(1,44) = 7.59, $p = .009, \eta^2 = .15$</td>
<td>F(1,44) = 11.85, $p = .001, \eta^2 = .21$</td>
</tr>
<tr>
<td>TX 1 min</td>
<td>2.54(1.54)</td>
<td>3.94(1.39)</td>
<td>F(1,44) = 23.17, $p &lt; .001, \eta^2 = .35$</td>
<td>F(1,44) = .04, $p = .17, \eta^2 = .04$</td>
</tr>
<tr>
<td>CX 3 min</td>
<td>2.88(1.65)</td>
<td>3.40(1.46)</td>
<td>F(1,44) = .11, $p = .70, \eta^2 = .03$</td>
<td>F(1,44) = 1.95, $p = .17, \eta^2 = .04$</td>
</tr>
<tr>
<td>TX 3 min</td>
<td>2.85(1.20)</td>
<td>2.28(1.32)</td>
<td>F(1,44) = 4.14, $p &lt; .05, \eta^2 = .09$</td>
<td>F(1,44) = 1.11, $p = .30, \eta^2 = .03$</td>
</tr>
<tr>
<td>CX 5 min</td>
<td>1.83(1.56)</td>
<td>2.50(1.57)</td>
<td>F(1,44) = 1.47, $p = .23, \eta^2 = .03$</td>
<td>F(1,44) = 1.92, $p = .17, \eta^2 = .04$</td>
</tr>
<tr>
<td>TX 5 min</td>
<td>1.06(1.85)</td>
<td>2.15(1.51)</td>
<td>F(1,44) = 1.47, $p = .23, \eta^2 = .03$</td>
<td>F(1,44) = 1.92, $p = .17, \eta^2 = .04$</td>
</tr>
<tr>
<td>CX 7 min</td>
<td>1.25(1.36)</td>
<td>1.67(1.43)</td>
<td>F(1,44) = 4.14, $p &lt; .05, \eta^2 = .09$</td>
<td>F(1,44) = 1.11, $p = .30, \eta^2 = .03$</td>
</tr>
<tr>
<td>TX 7 min</td>
<td>.65(0.69)</td>
<td>1.75(1.33)</td>
<td>F(1,44) = 1.47, $p = .23, \eta^2 = .03$</td>
<td>F(1,44) = 1.92, $p = .17, \eta^2 = .04$</td>
</tr>
<tr>
<td>CX weal</td>
<td>3.10(0.47)</td>
<td>3.20(0.39)</td>
<td>F(1,44) = 4.14, $p &lt; .05, \eta^2 = .09$</td>
<td>F(1,44) = 1.11, $p = .30, \eta^2 = .03$</td>
</tr>
<tr>
<td>TX weal</td>
<td>2.88(0.60)</td>
<td>3.31(0.42)</td>
<td>F(1,44) = 1.47, $p = .23, \eta^2 = .03$</td>
<td>F(1,44) = 1.92, $p = .17, \eta^2 = .04$</td>
</tr>
</tbody>
</table>

Main effects of Session (placebo effects) were demonstrated on reported itch at one, three, and five minutes, with less itch in the treatment session, compared to the control session (Figure 3.6) No effects were demonstrated for itch at seven minutes, or for weal size (Figure 3.7).
At one minute, Allergies was significant, with follow-up tests revealing that those without allergies \( n = 32, M = -0.89, SD = 1.74 \) had a reduction in itchiness from control to treatment sessions, whereas those with allergies \( n = 16, M = 0.84, SD = 1.58 \) had a slight increase. The small cell count (see Table 3.2) precluded fully testing for interactions between Allergies and Order.

Order was a significant predictor of itch at one minute, and of weal size. In both cases, those who had the control session first (Group 1) had less itch in the treatment session, compared to the control session, and those in Group 2 had an increase from control to treatment sessions (Table 3.3).

Allergies and changes in negative mood did not contribute to any of the other outcomes.

Figure 3.6 Average reported itch at 1, 3, 5 and 7 minutes post-histamine administration by session (control versus treatment). Error bars are standard error of the mean.
3.3.5. Discussion

This study investigated whether a suggestive placebo protocol could induce a placebo effect in local inflammatory skin reactions. The placebo manipulation was successful in reducing self-reported itch from control to treatment session, the order of session notwithstanding. No placebo effect was demonstrated on weal size; however, there was an order effect, with a reduction in weal size from control to treatment only in the group that underwent control procedures first.

To date, this is the first study to demonstrate a placebo effect on histamine induced inflammatory reactions when using only verbal suggestion. Prior work has shown that verbal suggestion can enhance learning protocols to produce placebo effects on itch [189]; but previous studies that attempted to modulate inflammatory skin reactions by suggestion alone have not been successful [161, 195]. In these earlier studies however, the verbal suggestions accompanying the placebos appear to have been both briefer, and less explicit. In contrast, participants in the current report watched a video and read an information sheet that described how the ‘antihistamine’ worked to suppress and block the effects of the histamine. Thus, it may be that more directive and descriptive manipulations are more effective in generating effects on itch. Similar interpretations have been offered for the variable effectiveness of suggestion-based hypnotic paradigms [204].
Order effects were observed in weal size and itch at one minute after the administration of histamine. Those who underwent the control session first had a reduction in itch and weal size, whereas those who attended the treatment session first had a slight increase. As noted earlier, some expectation-induced placebo effects work by activating top-down regulatory pathways [40]. However, for expectations to generate such processes, not only is conscious awareness needed [123], but a concrete representation of the suggested changes may be necessary. For example, while the experience of itch in general is common, the experimental induction of a histamine-induced skin reaction is likely to be a novel experience for most participants. As such, it was only after having had the experience of the skin reaction that participants’ were able to appropriately self-regulate their response. At the time of the one minute measure, only those who had already experienced the skin reaction in the control session were able to regulate the experience of itch. By the three and five minute measures, those receiving the ‘treatment’ in the first session also had a concrete representation of the stimulus. Thus, a concrete understanding of the suggestive instruction may be needed to modify inflammatory skin reactions by verbal suggestion alone.

The possibility that these order effects are due to regression to the mean or habituation to the protocol (i.e., a reduction from the first to the second laboratory visit regardless of session type) must be acknowledged. While mood states can influence histamine induced skin reactivity [200] and relaxation has been linked to reductions in hypersensitivity reactions [205], in the current study negative mood increased from session one to session two across both groups, which complicates an interpretation based on habituation or anxiety reduction [206]. It may be that the observed reduction reflects the additive effect of time on top of the receipt of ‘treatment’ with the suggestion of a reduced reaction.

The lack of a placebo effect in weal size could also reflect the relatively crude measure of weal size employed here. Measuring weal size has been shown to be methodologically difficult, with the identification of an accurate and consistent measure remaining elusive [207]. A further limitation to this study is that the sample was young and healthy, and the findings may not be translatable to an older population or patient groups. Relatedly, the histamine-induced inflammatory skin reaction only approximates the allergic reaction by mimicking the latter phases of the physiological processes involved in allergic skin reactions [204]. Thus, findings from this study are not necessarily applicable to chronic or allergic skin conditions.
While the translation of experimental results to clinical settings remains a challenge for the field of placebo research, there are possible applications of the current findings. As noted, psychological factors contribute to the onset and exacerbation of skin conditions [6, 191, 208], and findings from the current study indicate that a cognitive process such as expectation may be able to reduce symptoms of inflammatory skin reactions. Placebo mechanisms, such as the use of suggestion to activate top-down regulatory processes, may be useful as adjunctive treatment for idiopathic and unresponsive skin conditions that generate high rates of healthcare utilisation and poorer quality of life [6].

In conclusion, this study is the first to demonstrate a placebo effect in the context of inflammatory skin reactions using verbal suggestion alone. Findings indicate that while self-reported itch can be modifiable by suggestion alone, it may not be sufficient to modulate a parameter such as weal size. Expectations are thought to exert effects on outcomes by activating top-down pathways; however, when using verbal suggestion, a concrete representation of the suggested changes may be needed for such self-regulatory activity to take place, and for effects to be shown on certain parameters. Applied clinically, this could indicate that in some cases solely verbal suggestions of benefit or symptom alleviation may be insufficient. Individuals may need to understand at an experiential level exactly what the suggested effects of an intended treatment are likely to be. Results such as these can inform future placebo research, but may also be applied clinically to better treat idiopathic skin conditions.
3.4. Interim commentary: from the laboratory to a naturalistic setting

The preceding study investigated the effect of placebo suggestion on inflammatory skin reactions, an area of research that has received comparatively little attention. The finding that placebo suggestion can reduce the experience of itch offers the possibility of clinical application in the management of conditions involving itch. However, as with Experiment I (Chapter 3.1), findings generated in a laboratory study with healthy individuals will not necessarily apply in clinical samples.

The use of a patient sample with a chronic itch condition, such as idiopathic urticaria or atopic dermatitis, would have offered more clinical utility but, at the same time, would have introduced heterogeneity to the sample. For example, the fluctuating nature of such conditions and individual differences in the current status, chronicity, and severity of symptoms, would have made it much harder to standardise between conditions; increased variability not due to the experimental manipulations; and made it harder to detect effects. The use of a larger sample, perhaps with recruitment based on the homogeneity of their condition and symptoms, would be one approach to overcome this limitation, but one that would have resulted in a substantially lengthier recruitment process. Additionally, while a meta-analysis recently found evidence that placebo treatments can decrease itch [188], at the time of the study no prior research had been able to demonstrate that verbal suggestion alone could modulate skin reactions. It would have been less ethical to test what was an unproven intervention on a patient sample.

Thus, research in this area must consider logistical and ethical issues as well as clinical utility. While experimental laboratory studies with healthy volunteers provide incremental evidence for placebo effects in relatively ‘untapped’ placebo contexts such as those described in Chapters 3.1 and 3.3, findings are still limited by their relative lack of clinical application. One issue impeding progress in this area is the predominance of paradigms in which noxious stimuli is administered and then alleviated in an acute laboratory setting. Conversely, when patients are prescribed medicine they often take it home and are expected to self-administer the treatment amongst the demands of daily life, an environment notably different from a laboratory. With only a handful of studies employing ‘take-home’ treatments [126, 209], the evidence for placebo effects in naturalistic settings is relatively scarce.

Thus, while the first two experimental studies extend the current literature, both are limited insofar as they were conducted with healthy samples and in the relatively artificial environment of a
laboratory, which likely represents a poor approximation of ‘real’ treatment milieus. A way to overcome these two related issues, is with a paradigm that employs a ‘take-home’ treatment and a sample that is physically healthy but symptomatic or suffering from sub-clinical levels of a condition that may be amenable to placebo treatments. For example, stress, anxiety, and depression are pervasive and debilitating problems for individuals as well as for the public healthcare system. The stress and anxiety that arise from the demands and challenges of life can generate psychological distress and noxious symptoms, which provides an opportunity to investigate placebo effects in this context without deceiving a vulnerable patient population. Experiment I demonstrated that placebo treatments can enhance recovery from acute laboratory-based stressors; however, no research to date has investigated whether placebo treatments can be effective for the alleviation of general psychological distress with a take-home placebo treatment designed for use in a more naturalistic environment.

The final study (Experiment III) thus aimed to contribute building blocks to the bridge between scientific research and clinical application by using a physically healthy sample to investigate whether a more naturalistic placebo protocol could alleviate stress, anxiety, and symptoms of depression arising from general life stress.
3.5. The placebo effect in the context of stress, anxiety, and depressive symptoms in a non-laboratory setting.


3.5.1. Abstract

**Background.** With a healthcare system burdened by symptomatic and mental-health related conditions, the placebo effect may represent a useful clinical tool. First, however, there is a need to broaden research attention and investigate placebo effects outside the laboratory and beyond experimental pain. This study investigated the effectiveness of a take-home placebo treatment in the short-term alleviation of stress, anxiety, and symptoms of depression in a non-patient population.

**Method.** A sample of 77 participants was randomized to either the: ‘oxytocin’ treatment group (n = 22), the ‘serotonin’ treatment group (n = 22), or the wait-list control group (n = 33). The two treatment groups were given an ‘anti-stress treatment spray’ (placebo) to self-administer for three days, and completed online measures of perceived stress (Perceived Stress Scale-10), anxiety (Cognitive Somatic Anxiety Questionnaire), and symptoms of depression (Centre for Epidemiological Studies – Depression) before and after the three day protocol. **Results.** Both the ‘serotonin’ and ‘oxytocin’ treatment sprays were effective in reducing symptoms of depression; however, only those in the ‘oxytocin’ group reported less stress and anxiety as compared to controls. Overall the ‘oxytocin’ was perceived as more effective. **Conclusions.** Placebo effects can be translated to a real-life setting in the short term reduction of stress, anxiety, and symptoms of depression in a non-patient population. In treating psychological distress, placebo treatments may be useful addition to the treatment repertoire. The information given with treatment may be an important consideration for practitioners.
3.5.2. Introduction

Psychiatric and psychologically-influenced conditions represent a significant healthcare burden [1-4]. Treating ailments such as stress, anxiety and depression can be difficult, not only because they are pervasive and debilitating [9, 10], but because standard care pharmacological approaches may not always be optimal or effective. For example, in some cases, antidepressants may not deliver benefits over no-treatment in the long term [13] and there can be negative effects associated with long term medication use [11, 12].

The placebo phenomenon has shown that the act of administering treatment, regardless of its properties, can deliver health benefits [121, 147]. An individual’s expectations, the therapeutic ritual, and the psychosocial context of treatment [22, 26, 27], can generate positive changes in the absence of pharmacological agents. Thus, placebos could be a clinically useful tool; however, before the power of the placebo can be harnessed in mental-health contexts, further research is needed.

One issue to be overcome is that placebo effects are not often directly investigated in depressed and anxious patients because of the ethical issues inherent to deceiving vulnerable populations [29]. Despite this challenge, research shows that in the treatment of depression placebos used adjunctively with supportive care sessions can be just as effective as ‘active’ medications [210]; and meta-analyses of clinical depression trials report that for people who are mildly to moderately depressed, antidepressants over little benefit over placebos [211, 212]. Further, placebo responses in clinical trials for anxiety disorders can be up to 60%, with long lasting and clinically relevant effects observed in some trials [213]. However, the absence of direct placebo investigations in this area means one cannot be sure of the efficacy of stand-alone placebo treatments. That is, like drug trials that use placebo control arms to determine the efficacy of a pharmacological agent, the efficacy of a placebo treatment also needs to be specifically tested, ideally against a ‘no-treatment’ control.

Another issue hindering the translation of the placebo effect for clinical utility is the predominance of research carried out in laboratories. Such research offers experimental control and the ability to implement rigorous protocols, but represents a relatively artificial environment. Placebos have been shown to reduce acute stress and anxiety in lab settings [113, 164, 214]; however, in the real-world, depressed, stressed, or anxious patients are required to self-administer treatments around their daily activities and amidst the natural fluctuations in the demands and challenges of life. As a
consequence, effects seen in laboratory-based placebo experiments when acute noxious stimuli are induced and then alleviated with placebo treatments may not extend to real-life settings.

There have been relatively few studies investigating the effectiveness of placebo treatments when they are ‘prescribed’ and taken home for use over several days. One study using such a protocol demonstrated clinically significant improvements in IBS [126]; however, it is not known whether this finding is translatable to mental-health conditions. Thus, in order to expand knowledge in this area without jeopardizing the wellbeing of a vulnerable patient sample, the current study aimed to investigate the effectiveness of a take-home placebo treatment for the short-term alleviation of stress, anxiety, and symptoms of depression in a physically healthy, non-patient population.

3.5.3. Method

Design, randomization and blinding

This was a randomized, controlled, non-laboratory study. All participants were randomized into one of three groups: a wait-list control group or one of two ‘treatment’ groups. The two treatment groups received ‘anti-stress’ intranasal treatment sprays to self-administer for three days. Both treatment sprays were placebos and contained only sterile saline (5%), but were described as two different ‘compounds’: one which stimulated the body to produce oxytocin and the other to produce serotonin (see Procedures). Two different treatments were offered as part of a larger research study investigating personality predictors of responding to treatment descriptions.

The research assistant (RA) who met with participants was not blind to group; however, all baseline and outcome measures were completed by participants via an online survey (i.e., not in the presence of the RA).

Participants

To recruit a sample with sub-clinical levels of psychological distress (stress, anxiety, and depressive symptoms), advertisements requesting healthy volunteers experiencing mild to moderate daily stress were placed around a hospital research department and on a university intranet. Of 238 who expressed interest, 109 (46%) returned the screening questionnaire. Of these, 93 met inclusion criteria of being 18 – 65 years of age, no diagnosed psychological conditions in the past 5 years, no medications (except those for acne and birth control), and no chronic illness (diabetes, multiple
sclerosis, cancer, rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, organ transplant, lupus, auto-immune or respiratory conditions). Of the 93 eligible participants, 90 completed the first questionnaire assessing demographics and personality. Of these 90, six could not be contacted to schedule an appointment, one did not appear for their appointment, and two withdrew from the study. Of the 81 that initiated the treatment protocol, two did not complete the daily measures, and two withdrew because of adverse reactions attributed to the intranasal spray. The final sample size was 77, with 33 participants in wait-list control, 22 in the ‘serotonin’ group, and 22 in the ‘oxytocin’ group.

The university’s review board (The University of Auckland’s Human Participants Ethics Committee) approved the study (UAHPEC ref: 010757) and participants provided written consent after reading a detailed description of the study and the procedures involved. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

**Procedure**

After completing screening, consent, and an online personality survey (reported elsewhere), participants were scheduled for one 15-minute session with the RA. The RA gave a brief overview of the study, explaining how participants would receive an ‘anti-stress’ treatment to reduce the symptoms and experience of stress and anxiety. After the RA checked exclusion criteria they informed participants to which of the three groups (Treatment S, Treatment O, or wait-list control) they had been allocated.

The Treatment S (‘serotonin’) group were told the spray contained a compound designed to increase levels of serotonin in their system and that serotonin helps regulate stress responses by suppressing negative stress hormones and generating positive moods. The Treatment O (‘oxytocin’) group were told their spray contained a compound designed to increase levels of oxytocin in their system, and that oxytocin is a hormone that helps regulate stress responses by promoting social engagement and generating feelings of trust and connectedness. The control group were advised that for five days they would complete the online forms only and then commence the treatment protocol with their choice of either the serotonin or the oxytocin treatment sprays.

This information was re-iterated within a brief (2 minute) video. After the RA demonstrated how to use the intranasal spray and explained how to complete the daily online measures, participants
were given their treatment pack. This pack included the appropriate intranasal spray and written instructions that re-iterated all the verbal information provided.

**Summary of protocol**

After their appointment (Day 1) all participants were sent a link to the first questionnaire, which assessed baseline (pre-treatment) perceived stress, anxiety, and depressive symptoms. On Days 2, 3, and 4, they completed a symptom report sheet assessing the experience of general stress-related symptoms. On Day 5 they again completed the measures of stress, anxiety and depressive symptoms (post-treatment measures). Adherence to the regime was assessed by self-report measures during the three treatment days, as well as on the final day.

For each day of the protocol, links to the online forms were emailed with the instructions to complete the forms at the end of the day. Once the 5-day protocol had been completed, the treatment group participants were thanked for their participation. The control group were informed that they could now commence taking the treatment. Upon completion of the protocol all participants received $20 in vouchers and were entered into a draw to win an I-PAD.

**3.5.4. Measures**

Prior to the laboratory session, participants completed an online questionnaire assessing general health (doctor visits in the last 12 months, perceived general health, height and weight to calculate body mass index (BMI)), basic demographics (age, sex, ethnicity), and personality traits. The personality data are outside the scope of the current paper and will be reported elsewhere.

**Stress**

*The Perceived Stress Scale (PSS) [215]* is a 10-item questionnaire designed to measure the extent to which participants perceive their lives to be stressful. Participants are asked to indicate on a 5-point scale how often ('never' to 'very often') they have thought or felt in certain ways in the last month. Scores were coded so that higher values indicated higher levels of perceived stress. Internal consistency for the PSS was good on Day 1 ($\alpha = .80$) and Day 5 ($\alpha = .86$).

**Depressive symptoms**
The Centre for Epidemiological Studies Depression Scale (CES-D) assesses depressive symptoms in the general population. Participants rated how often they experienced symptoms of depression in the last week on a scale from 0 ‘rarely/none of the time’ (<1 day) to 3 ‘most/all of the time’ (5-7 days). Internal consistency for the CES-D was good on Day 1 (α = .89) and on Day 5 (α = .90).

**Anxiety symptoms**

The Cognitive Somatic Anxiety Questionnaire (CSAQ) assesses both somatic and cognitive aspects of anxiety. Participants rate from 1 (not at all) to 5 (very much so) how much in the last week they had experienced somatic symptoms of anxiety (e.g., ‘I had diarrhoea’ and ‘my heart raced’) as well as anxiety related thoughts (e.g., ‘I worried too much over something that doesn’t really matter’). Internal consistency for the CSAQ was good on both Days 1 and 5 (αs = .85).

**Daily stress symptoms**

On Days 2, 3, and 4, participants completed a measure of stress symptoms. This 16-item scale was developed for the study and asked how much participants had experienced symptoms of stress during the day, from 0 ‘not at all’ to 7 ‘extremely’. For example, feeling ‘stressed out’, heart pounding or racing, felt sad or down, and inability to concentrate. The scale was designed to measure symptoms of stress, depression, and anxiety during the three days that the other measures were not administered. The internal consistency of the scale was good for all three days (Cronbach’s α = .90, .91, and .92).

**Dosage and adherence**

On Days 2, 3 and 4, those in the treatment groups completed a self-report measure of dosage: ‘how many times did you administer the spray today’ and ‘how many pumps of the spray in total did you administer today’. On Day 5 they completed a measure of overall dosage and adherence: they were asked to rate on a scale from 0 to 6: to what extent did you follow the recommended dose; and how many times did you forget a dose? They were also asked to indicate how many days did you administer the treatment spray (0 to 3); and on average how many times a day did you administer the treatment spray.
**Perceived effectiveness**

On the final day of the protocol, participants were asked to rate from 1 (‘not at all’) to 10 (‘very much so’) how much did the anti-stress treatment: reduce stress / reduce feelings of irritability / reduce the impact of life pressures / reduce feelings of tenseness and frustration / reduce symptoms of stress.

Using this same scale, participants also rated how much the treatment reduced stress by increasing feelings of social engagement and reduced negative stress-related moods. These two items were consistent with experimental suggestions provided regarding the effects of the oxytocin and serotonin treatments respectively.

**3.5.5. Results**

**Analysis**

One-way ANCOVAs were conducted to test hypotheses and to check for baseline differences. Two-tailed tests for significance were set at .05 and pairwise comparisons were corrected with LSD.

**Sample characteristics**

Participants were aged from 19 to 50 years of age ($M = 24, SD = 5.92$); predominantly female (70%); with NZ Europeans making up the largest ethnic group (53%) with Asian (including Indian, Sri Lankan, and Pakistani participants) the next largest group (40%) and the remainder describing themselves as ‘other’ (7%). There were no baseline differences in the outcome variables as a function of group.

While only a trend for a significant baseline differences was observed for age (Table 3.4), pairwise comparisons revealed a difference in age between the control and the serotonin group ($p = .03$). Age was thus added as a covariate in analyses.

**Placebo effects**

Three, one-way ANCOVAs were carried out to compare differences between the groups in their levels of stress, anxiety, and symptoms of depression on Day 5, while controlling for Day 1 scores, and age.

Results revealed a main effect of group for depressive symptoms (Table 3.4), with lower scores on Day 5 in both the serotonin and oxytocin groups as compared to controls ($p < .001$), but no difference between the two treatment groups ($p = .64$). For anxiety, there was a main effect of group at Day 5 (Table 3.4), but only those in the oxytocin group had lower anxiety scores than controls ($p <$
The serotonin group did not have lower anxiety than controls \((p = .11)\) but there was no difference between serotonin and oxytocin groups \((p = .17)\). Similarly, there was a main effect of group on perceived stress on Day 5; however, only the oxytocin group had significantly lower stress than controls \((p < .01)\), with a trend for the serotonin group to also report less stress \((p = .06)\). There was no difference between the two treatment groups \((p = .52)\).

Table 3.4.

Tests for baseline differences between the groups in demographic, health, and outcome variables; as well as tests for placebo effects on outcome variables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control ((n = 33))</th>
<th>Serotonin ((n = 22))</th>
<th>Oxytocin ((n = 22))</th>
<th>(\chi^2)</th>
<th>(p)</th>
<th>(r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% female)</td>
<td>22/33 (66%)</td>
<td>16/22 (73%)</td>
<td>16/22 (73%)</td>
<td>.33</td>
<td>.85</td>
<td>.07</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian vs non)</td>
<td>17/33 (52%)</td>
<td>12/22 (55%)</td>
<td>14/22 (64%)</td>
<td>.81</td>
<td>.67</td>
<td>.10</td>
</tr>
<tr>
<td>Age (M(SD))</td>
<td>22.15(3.46)</td>
<td>25.68(7.27)</td>
<td>23.59(6.92)</td>
<td>F(2, 74) = 2.44</td>
<td>.09</td>
<td>.06</td>
</tr>
<tr>
<td>BMI (M(SD))</td>
<td>22.76(3.12)</td>
<td>22.64(3.09)</td>
<td>23.41(5.89)</td>
<td>F(2, 74) = .24</td>
<td>.79</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Perceived health (M(SD))</td>
<td>14.53(1.61)</td>
<td>13.77(1.74)</td>
<td>14.64(1.81)</td>
<td>F(2, 73) = 1.75</td>
<td>.18</td>
<td>.05</td>
</tr>
<tr>
<td>Dr visits (12 mths) (M(SD))</td>
<td>2.97(3.79)</td>
<td>3.50(5.26)</td>
<td>4.00(3.78)</td>
<td>F(2, 74) = .39</td>
<td>.68</td>
<td>.01</td>
</tr>
<tr>
<td>PSS (Day 1)</td>
<td>30.33(5.13)</td>
<td>29.23(5.82)</td>
<td>30.91(5.46)</td>
<td>F(2, 74) = .55</td>
<td>.58</td>
<td>.02</td>
</tr>
<tr>
<td>CES-D (Day 1)</td>
<td>18.27(9.10)</td>
<td>17.73(8.82)</td>
<td>19.59(10.27)</td>
<td>F(2, 74) = .23</td>
<td>.79</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>CSAQ (Day 1)</td>
<td>33.33(9.24)</td>
<td>31.55(9.82)</td>
<td>35.77(13.01)</td>
<td>F(2, 74) = .88</td>
<td>.42</td>
<td>.02</td>
</tr>
<tr>
<td>PSS (Day 5)</td>
<td>29.63(5.95)</td>
<td>25.59(6.86)</td>
<td>25.63(5.85)</td>
<td>F(2, 71) = 4.00</td>
<td>.01</td>
<td>.12</td>
</tr>
<tr>
<td>CES-D (Day 5)</td>
<td>19.19(9.30)</td>
<td>13.77(9.91)</td>
<td>14.55(9.79)</td>
<td>F(2, 71) = 11.73</td>
<td>&lt;.001</td>
<td>.25</td>
</tr>
<tr>
<td>CSAQ D (Day 5)</td>
<td>30.84(8.41)</td>
<td>26.23(8.37)</td>
<td>28.17(9.35)</td>
<td>F(2, 71) = 5.02</td>
<td>&lt;.01</td>
<td>.12</td>
</tr>
<tr>
<td>Symptoms (avg)</td>
<td>2.84(.86)</td>
<td>2.15(1.00)</td>
<td>2.28(.87)</td>
<td>F(2, 70) = 3.09</td>
<td>.05</td>
<td>.08</td>
</tr>
</tbody>
</table>

A one-way ANCOVA was carried out to assess differences in average stress symptoms during the 3-day protocol (Days 2, 3, and 4), while controlling for age. There was a marginal main effect of group (Table 3.4). Pairwise comparisons revealed that both the serotonin and oxytocin groups reported fewer stress symptoms than controls \((p = .03\) and \(p = .047\) respectively), with no difference between the two treatment groups \((p = .87)\).

**Treatment adherence and perceived effectiveness**

Independent samples t-tests (two-tailed with significance set at .05) revealed a difference between the two treatment groups in perceived effectiveness. Those taking ‘oxytocin’ reported it more effective.
than ‘serotonin’ (Table 3.5). Further, compared with ‘serotonin’, taking ‘oxytocin’ increased feelings of social engagement (as per the suggestive instruction) whereas ‘serotonin’ failed to significantly reduce negative stress related moods (as per the suggestive instruction).

While non-significant, there was an overall trend for the oxytocin group to self-administer a greater number of dosages and be more adherent (Table 3.5). There were no significant correlations among adherence, dosage, and outcomes (ps > .05).

The control group was permitted to select their choice of the two treatments to commence upon completion of the wait-list protocol. A significantly greater proportion \( \chi^2 = 8.76, p < .01 \) chose to take ‘serotonin’ \( n = 25 \) than ‘oxytocin’ \( n = 8 \).

Table 3.5.
Results of Independent sample t-tests comparing the serotonin and oxytocin groups in adherence to the regime, as well as the perceived effectiveness of the treatment.

<table>
<thead>
<tr>
<th>Dosage and adherence measures</th>
<th>Serotonin M (SD)</th>
<th>Oxytocin M (SD)</th>
<th>t(42)</th>
<th>p</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived effectiveness</td>
<td>28.64(16.46)</td>
<td>37.45(12.04)</td>
<td>-2.03</td>
<td>.05</td>
<td>-.63</td>
</tr>
<tr>
<td>Reduced negative stress related moods</td>
<td>4.32(2.73)</td>
<td>5.41(2.34)</td>
<td>-1.42</td>
<td>.16</td>
<td>-.44</td>
</tr>
<tr>
<td>Increased feelings of social engagement</td>
<td>3.00(2.35)</td>
<td>5.55(2.42)</td>
<td>-3.54</td>
<td>.001</td>
<td>-1.09</td>
</tr>
<tr>
<td>No. times used the spray (recommended: 2 x day x 3 days)</td>
<td>7.09 (1.93)</td>
<td>8.15(2.46)</td>
<td>-1.56</td>
<td>.13</td>
<td>-.49</td>
</tr>
<tr>
<td>No. pumps (recommended: 4 x day x 3 days)</td>
<td>14.27(4.12)</td>
<td>16.35(5.00)</td>
<td>-1.47</td>
<td>.15</td>
<td>.46</td>
</tr>
<tr>
<td>Extent followed recommended dose (from 0 to 6)</td>
<td>5.50(67)</td>
<td>5.32(94)</td>
<td>-.74</td>
<td>.47</td>
<td>.23</td>
</tr>
<tr>
<td>How many times missed a dose</td>
<td>.23(.53)</td>
<td>.23(.43)</td>
<td>0.00</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>On average how many times a day administered spray (recommended 2 x day)</td>
<td>2.64(.95)</td>
<td>3.00(1.02)</td>
<td>-1.219</td>
<td>.23</td>
<td>.05</td>
</tr>
</tbody>
</table>

3.5.6. Discussion

This study investigated the effectiveness of a take-home placebo treatment in the alleviation of mild to moderate psychological distress. Findings revealed that in a non-patient population, placebos can be effective in a naturalistic setting and that a self-administered placebo treatment can reduce the symptoms of stress, anxiety, and depression across a short time frame. Both the serotonin and oxytocin placebo treatment groups had fewer depressive symptoms after the treatment protocol and reported fewer symptoms of stress during the three days of use, compared to the control group. Only
the oxytocin group reported less perceived stress and fewer symptoms of anxiety after the treatment, as compared with the control group.

The ‘oxytocin’ was not only more effective in reducing anxiety and stress scores, but was also subjectively rated as more effective overall. Prior work has shown that a patient’s belief in the effectiveness of their treatment is an important part of their actual effectiveness [218]. At face value however, ‘serotonin’ was a more attractive option, as the preferred treatment choice for the wait-list controls. Thus, at the end of the treatment protocol, despite the two treatments containing only saline, participants taking a compound they thought stimulated the production of oxytocin, was more effective.

A possible explanation for the superiority of the oxytocin treatment might be the buffering qualities of perceived social support. Those in the oxytocin group were told it would stimulate feelings of social engagement and, indeed, this group reported greater feelings of social engagement after the treatment. Perceived social support can ameliorate symptoms of anxiety [219] and attenuate the impact of stressors in laboratory contexts [220]. Social support may be a buffer that prevents stress leading to depression [221], and social networks and social connectedness have been repeatedly linked to better outcomes in depression [10, 222]. Self-administering ‘oxytocin’ may thus have created a greater subjective experience of being socially engaged or, more speculatively, prompting participants to actually engage more in social interactions. Whether from a perceived or actual increase in social engagement, participants appear to have experienced benefits. Future research might test this distinction by employing objective behavioural measures of social interaction, and more comprehensive measures of perceived social support.

More broadly, the question of how to transfer placebo effects into clinical contexts represents a substantial ethical and practical hurdle [100, 193]. Prior work has shown how placebos can be used adjunctively to support therapeutic interventions in a depressed sample [210] but most evidence for the placebo effect in this area arises from clinical drug trials. In the current study a non-patient sample was recruited which limits the clinical applicability; however, the baseline depression scores were high, with the average across the whole sample above the standard screening cut-off point of 16 [216]. In recruiting a sample of individuals experiencing life stressors, the observed high baseline scores of depressive symptomology are not surprising. Together, this increases confidence that these findings offer clinical utility, and at least might be applicable to mildly depressed students, who are known to experience higher rates of moderate psychological distress [223].
Findings from the current report indicate that placebos can generate short-term improvements in symptoms of distress, which offers another way in which placebo effects might be leveraged. That is, with a delay before most anxiety and depression medications take effect, placebos could be used as an interim treatment so that patients experience some form of immediate relief. Equally, when a drug washout phase is required between medications, a placebo could be used as a stop-gap measure, so that patients do not feel abandoned or despairing while waiting for a new medication to take effect.

Clearly, care would need to be taken so that treatments are presented without deception while still generating an expectation of benefit; however, a prior study has demonstrated how this delicate balance can be achieved. Clinically significant improvements in IBS symptomology were shown after participants were told they had been given an inert substance, but expectations of clinical improvement were still created by informing patients that the treatment has ‘been shown in rigorous clinical testing to produce significant improvement in IBS symptoms through mind-body self-healing processes.’ [126 p. 2]. It seems reasonable to suspect that similar benefits might obtain for the mental health outcomes evaluated in this report.

Findings also indicate that placebos could be useful for assisting with treatment of sub-clinical levels of stress, depression and anxiety in primary care. In the current study, the verbal suggestion focussed on the stress-reducing properties of the treatment spray, but it had the effect of reducing overall psychological distress, and in particular, depressive symptoms. There are clear overlaps between perceived (or psychological) stress, anxiety and depression [221], with chronic stress and a dysregulated physiological stress system a factor in the development of depression [224]. This finding suggests that for individuals feeling challenged by life stressors, targeting the experience of stress may have the flow-on effect of alleviating depressive symptomology.

Overall, with a plethora of evidence that includes neuro-scientific research [225], it is now possible for clinicians to truthfully advocate the efficacy of placebos. Describing to patients how placebos work, such as stimulating the brain to release neurotransmitters [45] and activating endogenous healing processes [226], may be a useful way to explain how supposedly ‘inert’ treatments can exert real effects on health outcomes. Further work using open-placebo designs is needed to explore how physicians and clinicians can ethically and optimally offer placebos to patients as a treatment option.
Limitations to the current study include the use of a healthy, mostly young, non-patient population, which limits the generalizability and applicability of findings. Findings are also limited by the short time frame. It is not known whether effects would be the same for a longer treatment period, or how they might hold up over time. Future research could aim to replicate findings in a patient population and across a longer time period.

3.5.7. Conclusion

Overall, findings suggest that placebo effects can be translated to a real-life setting in the reduction of moderate stress and symptoms of anxiety and depression, at least in the short term. With a healthcare system that is plagued by overtaxed resources and over-medicated individuals, new ways to treat psychological distress while minimizing iatrogenic harm are needed. The placebo effect represents a health tool that could be harnessed for clinical benefit in mental-health related ailments.

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Declaration of conflicting interests

The Authors declare that there is no conflict of interest to report.

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3.6. Summary: suggestion-induced placebo effects in non-pain paradigms

The preceeding paper described how a self-administered take-home placebo treatment can reduce stress, anxiety, and depressive symptoms in a non-laboratory setting. The use of a physically healthy but stressed sample reduced the risk of harming a vulnerable population, while providing a closer approximation to the sort of sample and level of symptomology for whom such a placebo treatment might be safely employed. Further, with participants taking the treatment home for self-administered use, the protocol more closely resembled a standard medical treatment regime and thus offers findings that are more ecologically valid in terms of both the typical administration modality (self) and context (home) in which treatments are administered.

The work documented in this thesis so far has shown how placebo treatments can enhance acute physiological stress recovery in an experimental setting, reduce the experience of itch, and alleviate the symptoms of stress, anxiety, and depression when self-administered outside the laboratory setting. These studies offer incremental contributions to the placebo literature while concurrently addressing several limitations evident in placebo literatures to date.

First, all three studies demonstrate suggestion-induced placebo effects in non-pain paradigms, thus answering the first research question. Second, the finding that placebo suggestion can influence heart rate variability (Chapter 3.1) contributes to a smaller body of research demonstrating that placebos can exert effects on objective outcomes, the relative dearth of such research a criticism of the extant literature. Third, that placebo suggestion alone can reduce itch and thus modulate short-term inflammatory skin reactions (Chapter 3.3) had not not been previously shown and, as such, represents a novel contribution to this field. Finally, the demonstration that a self-administered placebo treatment can be effective for psychological distress in a naturalistic setting (Chapter 3.5) is one of only a few such studies, thus helping to fill a gap in the literature and provide an initial foundation for bridging basic laboratory work and clinical application. Overall, the collective data from these three studies demonstrates that placebo effects are indeed evident beyond the pain context, and that placebo treatments could be clinically useful in assisting with the alleviation of symptoms associated with allergic skin conditions, psychological stress, depression, and anxiety.

Limiting the utility of these (and other) findings, however, is the fact that not everyone responds to placebos [227]. High variability in response rates and effect sizes across different placebo
studies [50] partially reflects study design and the different conditions within which placebo effects are investigated [64, 228]. However, variation may also reflect differences in individual response rates within a given trial [227]. That is, using the group average to determine the presence of a placebo effect (e.g., the mean change in the placebo condition as compared to the mean change in the control condition), may mask individual differences in placebo responding.

This consideration suggests that in the preceding papers as well as in the literature more broadly, rather than the presence of a uniform placebo response it is likely that some individuals are responding to the placebo manipulation, whereas others are not. Understanding such variation is an essential development in the attempt to leverage the placebo effect for clinical benefit. While it is important to demonstrate that placebos can exert effects on particular parameters and in different settings, it also necessary to determine who might be responsive to placebo treatments. If there are stable and measurable endogenous variables (i.e. personality traits) associated with the tendency to respond to the mere suggestion of benefit, then there is clear clinical utility in identifying those variables. Such identification is also useful for scientific research, with the efficacy of pharmacological agents more easily detectable once responses to the placebo aspects of treatment are better controlled.

The next chapter of the thesis introduces the second research question, the issue of which personality characteristics predict responding to placebo treatments. This question is considered by first defining personality, then by evaluating the current state of placebo personality literature, and finally by identifying and addressing limitations to this literature.
4. THE POSSIBLE ‘PLACEBO-PRONE’ PERSONALITY

To date, the identification of consistent personality traits predictive of placebo responding has been elusive [227] and represents a gap in the large placebo literature. This issue, the possible ‘placebo prone’ personality, constitutes the second research question of the doctoral research programme presented here. To introduce and to initiate commentary on this question, personality is first briefly described and defined before an assessment of the extant placebo personality literature is presented in the context of a systematic review.

4.1. Personality

That humans have characteristic and identifiable patterns of behaviour is, like the placebo, an ancient concept. More than 2000 years ago, Hippocrates asserted that there are four ‘humors’ of the body, representing four temperament types, with excesses of these fluids influencing mood and behaviour [229, 230]. Now, the literature on human personality is gargantuan and complex, reaching far and wide into multiple research domains [231].

At least some of the complexity in this field arises from the different approaches to the study of personality, such as looking at traits versus motives, cognitions or social contexts [232]. There is disagreement about the basic dimensions of personality [233], whether theory should explain or describe personality [234] and/or whether traits endure across different situations or are context-dependent [231]. Given this complexity and the nature of the current research question, a protracted discussion of personality theory is outside the scope of this thesis.

That said, a working characterisation is necessary. Hence, for the purposes of this research, personality will be defined as the ‘more or less stable and enduring organisation of a person’s character, temperament, intellect, and physique which determines their unique adjustments to their environment’ [235 p. 2]. While there may be nuanced differences in personality nomenclature, in this thesis, terms such as such as ‘personality’, ‘trait’, and ‘disposition’ (or ‘dispositional style’), will be considered interchangeable.
With personality defined as relatively stable response tendencies, consideration of the possibility of a placebo personality offers a way of characterising and even predicting patterns of responding to placebo treatments. The identification of those individuals who might be dispositionally responsive to placebo treatments could potentially advance scientific research and enhance the clinical utility of the placebo phenomenon [236]. To initiate investigation into this issue of who might be responsive to placebos, a systematic review of the personality variables that have been associated with placebo responding was conducted, as described next. This review took place in the early stages of the doctoral programme so that findings could inform subsequent empirical investigations, as detailed in the sections to follow.

4.2. Systematic literature review

4.2.1. Background
The notion of a placebo-prone personality was perhaps first suggested over 70 years ago [237], following reports of an U-shaped distribution in responses to a pharmacologically inert headache treatment [238]. A number of subsequent attempts to identify consistent personality predictors of placebo responding were unsuccessful [227] and led to doubts as to the existence of a placebo personality [58, 239-241].

More recent commentary however, suggests that early efforts may have been affected by limitations such as the use of retrospective measurement approaches, non-experimental studies, and inadequately designed trials [227]. For example, a key limitation was the lack of adequate controls. As noted in Chapter 2, without comparison to a control condition, natural fluctuations in the experience of pain may have been incorrectly attributed to the placebo effect [242-245]. Without demonstration of a true placebo effect, personality variables associated with fluctuations in symptoms after administration of a placebo cannot be considered indicative of placebo responsiveness. Relatedly, the failure to identify personality variables associated with such fluctuations is not indicative of the lack of a ‘placebo-prone’ personality.

Over time, however, the placebo literature has matured and become more sophisticated in terms of conceptual development as well as technological advancement. A larger number of studies are now conducted with the specific aim of investigating true placebo effects, thus better enabling the
drawing of inferences about possible relationship between placebo responsiveness and personality traits. Additionally, more recent research using neuro-imaging techniques has linked the neural pathways associated with certain personality traits to placebo analgesic responses [246]. Further, genetic variants have been found to be related to placebo responses in treatments for social anxiety [247], major depressive disorder [248], and irritable bowel syndrome [249]. With the use of appropriate study designs (i.e., those able to detect true placebo effects) and the measurement of stable variables (e.g., genotypes) these findings suggest that there may be enduring endogenous variables that are indicative of placebo responsiveness.

In sum, the methodological issues limiting prior placebo personality research, coupled with findings from these more recent studies, suggest it is worth revisiting this notion. As such, a systematic review of the personality variables that have been associated with placebo responding was conducted as described next.

4.2.2. Search procedures

Search and review procedures took place from 1 May 2012 to 30th June 2012 and followed the PRISMA guidelines [250]. Note, while it was possible to update this search at a later point in the doctoral programme, a decision was made to retain the integrity of the original search because the development of the Transactional Model of Placebo Responding (see Chapter 5.1) flowed directly from the results of this search and reflected the state of the literature at that time. Moreover, later updates to the search would have compromised the integrity of the paper that was subsequently published during 2013-2014. However, studies germane to the question at hand that were published after the search have been added to the results table, noted as such, and are commented on in the general discussion below.

As a starting point for the search, articles citing the 2008 paper ‘Do placebo responders exist?’ [227] were assessed to check whether any subsequent reviews had taken place. With no reviews located, a systematic computer based search was conducted in the electronic databases Medline, Web of Science, PsycINFO and SCOPUS, using the inclusion criteria: English language; human studies; 1 January 1970 – 31st December 2012; published, peer reviewed articles.

The advanced search function within each database was used to combine ‘placebo effect’ and ‘placebo response’ with personality related descriptor variables (‘personality’, ‘disposition’, and ‘trait’).
To minimise the return of placebo controlled drug studies, the search variable ‘NOT placebo controlled’ was added. For example (with the imposition of inclusion limits noted above) the syntax for a Web of Science search was:

\[
\text{Topic=}("\text{placebo effect}\") \text{ AND Topic=}(\text{personality}) \text{ NOT Topic=}(\text{placebo-controlled})
\]

\[
\text{Timespan=}1970-01-01 \text{ - } 2012-12-31 \text{ (Processing Date). Databases=} \text{SCI-EXPANDED, SSCI.}
\]

Then, given that studies may have investigated specific personality variables based on previous findings, specific searches for each of the trait variables identified (Table 4.1) were carried out by combining ‘placebo effect’ and ‘placebo response’ (respectively) with the identified personality constructs.

Table 4.1.
Systematic search exclusion criteria with reasons for each criterion.

<table>
<thead>
<tr>
<th>No.</th>
<th>Exclusion criteria</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Non-empirical commentary.</td>
<td>Reviews or theoretical pieces that offer a general commentary rather than presenting the data of interest (experimental/empirical demonstration of personality variables associated with placebo responding).</td>
</tr>
<tr>
<td>2</td>
<td>‘Placebo-controlled’ trials where placebos were used as controls for a drug trial.</td>
<td>Studies not designed to investigate placebo effects specifically may not generate ‘true placebo effects’ and are therefore not a ‘placebo study’.</td>
</tr>
<tr>
<td>3</td>
<td>No placebo manipulation.</td>
<td>Without administration of a placebo treatment for benefit, placebo effects can only be inferred.</td>
</tr>
<tr>
<td>4</td>
<td>Studies without adequate controls</td>
<td>True placebo effects cannot be determined.</td>
</tr>
<tr>
<td>5</td>
<td>Studies without use of psychometric and standardized measures of traits.</td>
<td>Factors not assessable by psychometric means (i.e., use of only genotyping or neuroimaging measures) are outside the scope of the research question. Non-standardised measures (i.e., qualitative interviews) do not provide comparable data. Measures of trait-like variables (e.g., self-efficacy) are not enduring enough for inclusion.</td>
</tr>
<tr>
<td>6</td>
<td>Nocebo studies.</td>
<td>Outside the scope of this research programme.</td>
</tr>
</tbody>
</table>

Articles generated from these searches were reviewed for relevance by first reading the article title then, if necessary, the abstract and/or methods. Retained studies were scored on several criteria (Appendix A), to enable an assessment of their design, methodology, and measurement approaches. No meta-analytic techniques were employed to assess or compare findings and effects sizes (e.g., risk ratios, difference in means) because this was not the focus of the review. Effect sizes were not reported or commented on because the size of a placebo effect is known to vary depending on a number of factors [25] and was not the focus of the review. The principal summary measure was a
simple count of the studies that had found associations between each personality variable and placebo responses (Table 4.2).

4.2.3. Results

Of 479 studies initially identified, 442 were excluded for one of three main reasons: (1) not a placebo study (51%); (2) represented a non-empirical article (36%); or (3) did not measure personality (13%). After manual inspection of methods, 22 of the remaining 37 (59%) were excluded because they did not employ a psychometric assessment of a dispositional trait (Table 4.1). Fifteen studies were ultimately included in the review (Appendix A), and several constructs related to placebo responding were identified as summarised below.

Table 4.2.
Summary of evidence for those constructs empirically linked to placebo responding with overall number of studies (k), pooled sample sizes (pooled N), the proportion demonstrating a relationship with personality, and the condition or context in which the placebo manipulation took place.

<table>
<thead>
<tr>
<th>Trait</th>
<th>k</th>
<th>Pooled N</th>
<th>Ratio of sig finding</th>
<th>Condition or context of placebo manipulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>4</td>
<td>290</td>
<td>1/4</td>
<td>Pain, itch &amp; pain, MS symptoms, cognitive performance</td>
</tr>
<tr>
<td>Acquiescence</td>
<td>2</td>
<td>312</td>
<td>1/2</td>
<td>Pain, psychological distress</td>
</tr>
<tr>
<td>Dopamine trait</td>
<td>1</td>
<td>22</td>
<td>1/1</td>
<td>Pain</td>
</tr>
<tr>
<td>Empathy</td>
<td>1</td>
<td>48</td>
<td>1/1</td>
<td>Pain</td>
</tr>
<tr>
<td>Extraversion</td>
<td>3</td>
<td>399</td>
<td>2/3</td>
<td>Pain, IBS, cognitive performance</td>
</tr>
<tr>
<td>Optimism</td>
<td>5</td>
<td>525</td>
<td>3/5</td>
<td>Pain, sleep quality, cognitive performance, well-being</td>
</tr>
<tr>
<td>Suggestibility</td>
<td>3</td>
<td>221</td>
<td>2/3</td>
<td>Pain, itch &amp; pain, pulmonary function</td>
</tr>
</tbody>
</table>

Absorption: a positive relationship was found between placebo responding and symptom improvement in multiple sclerosis patients [251]; however absorption was unrelated to placebo responses in three other studies [195, 252, 253]. Acquiescence: higher acquiescence was related to a greater placebo response in symptom reporting [254], but not in pain [253]. A ‘dopamine-related’ trait was found to be associated with the placebo analgesic response* [246]. Empathy: a link between placebo analgesic responding and empathic concern was found [95]. Extraversion: being extraverted and having an empathic practitioner predicted placebo responding in irritable bowel syndrome symptoms [127], but not in cognitive performance [252]. Optimism: was related to reductions in self-reported pain [255] and improvements in self-reported sleep [256] but not in cognitive performance [252] or in ‘well-being’
Optimism, extraversion and state anxiety interacted to predict placebo analgesic responding* [257]. Submissiveness: placebo responders were reported to be more submissive than non-responders [165]; however, this trial was inadequately controlled. Suggestibility: highly suggestible individuals had greater placebo responses in pain* [258], and pulmonary function [135] but suggestibility was not related to experimentally-induced itch and pain [195]. No relationships were found for neuroticism or negative affect [127, 195, 252, 257]; however, one study reported a trend towards higher negative affect in high placebo responders [251]. Social desirability was consistently unrelated to placebo responding [195, 256, 257]. Spirituality only related to responses to a placebo sleep therapy treatment when positioned so it was concordant with spiritual beliefs [240].

Since the review was completed, three studies that meet inclusion and exclusion criteria have been published. These studies were not included in the search procedure described above as explained earlier, but have been added to the results table (Appendix A) as an addendum. In summary: empathic concern was related to placebo analgesic responses in a social observational paradigm [259], ego resiliency, low hostility, altruism, and straightforwardness [260] were related to greater placebo analgesic responses, as was openness to experience* [157]. These three studies were all carried out in the context of experimentally-induced pain.

Note, four of the above studies (indicated in the text with asterisks) employed learning protocols, in which the participant learned, or learned to expect, less pain with a placebo cream via the surreptitious pairing of a reduced pain stimulus with the application of the placebo. Thus these links between a ‘dopamine-related’ trait [246], openness [157], suggestibility [258], and optimism and extraversion [257] were not generated by solely suggestive placebo protocols, which is the focus of this thesis. However, the complexities associated with separating learning from expectations (see Chapter 2.3), makes it difficult to determine whether personality predictors of responding to learning protocols should be separated from those employing verbal suggestion alone. Given that the number of studies meeting inclusion/exclusion criteria was small, the findings from those studies employing learning protocols have been included here, with the caution that studies using different paradigms might not be directly comparable. Future research might aim to investigate whether there are differences in personality types responding to learning versus suggestion-based protocols.

Overall, the search revealed links between placebo responding and several traits; however, findings are scattered and inconsistent (Table 4.2). Upon critical review of the studies (Appendix A),
two key limitations are apparent. First, a lack of theoretically-driven research may be hindering progress, and some sort of conceptual framework to organise findings to date is needed. This limitation is addressed in the following chapter which organises findings from the literature review into a new conceptualisation of placebo responsiveness. Second, there is a dearth of research into the placebo personality outside the context pain - a limitation which is addressed later (Chapter 6), with two papers documenting personality predictors of placebo responding in the context of stress recovery (6.1) and itch (6.3).
5. CONCEPTUALISING PLACEBO RESPONSIVENESS

A key limitation identified from conducting the systematic literature review was the need for more theoretical input into the search for the placebo personality. Within this limitation, there are two related issues that need to be addressed. First, the review identified that a number of different traits have been associated with placebo responding, a finding which may suggest that placebo responsiveness is not confined to a unitary trait. Second, and perhaps the most salient aspect, is the observation that the extant placebo personality research does not appear to draw on personality theory to guide design, measurement choices, or hypotheses. Instead, personality traits are often assessed in an attempt to replicate prior findings or because of a neuro-anatomical relationship between traits and placebo pathways (see Appendix A). While these represent valid scientific approaches to formulating hypotheses, the use of an appropriate theoretical framework is also important.

In personality research, a distinction has been made between inter-individual versus intra-individual approaches, in which personality is considered to be either (respectively) stable across different situations, or a function of an individual’s neurobiological predispositions to respond in certain ways to environmental stimuli [234]. Findings from the systematic literature review described in the previous chapter suggest that characterising placebo responsiveness as a unitary trait that endures across multiple situations may not be the most appropriate, useful, or generative conceptualisation.

Contradicting this unitary, inter-individual approach is the fact that a number of distinct traits have been associated with placebo responding (Table 4.2) and inconsistencies exist across different placebo contexts. For example, as noted earlier, optimism has been associated with placebo effects in experimental pain and IBS symptoms, but not in cognitive performance; and absorption was associated with placebo responses in MS symptoms but not in the context of experimental pain. Thus, it appears that despite the accepted role of contextual factors in generating placebo responses [22] and the possible interaction between disposition and environment already reported in the literature [256], this issue has not been comprehensively considered. In sum, findings suggest that the lack of theoretically-driven research into the placebo personality could be hindering progress, and a new conceptualisation of placebo responsiveness may be useful.
5.1. A new conceptualisation of placebo responding


5.1.1. Abstract

The placebo effect is now recognised as a genuine psychobiological phenomenon; however, the question of how it can be systematically harnessed to improve health outcomes is not yet clear. One issue that remains unresolved is why some respond to placebos and others do not. A number of traits have been linked to responding, but findings are scattered. In extending prior work, this paper offers three considerations. First, attempts to describe the placebo responder via a single personality trait may be limiting. A synthesis of findings to date suggest placebo responsiveness may reflect a two faceted construct, with ‘inward’ and ‘outward’ orientation representing the different but related facets of placebo responsiveness. Second, the lack of theoretically driven research may be hindering progress. Personality measures rather than personality theory appear to be driving research and higher order traits are descriptive tools with limited use in predicting behaviour. A biologically based stimulus-response model of personality that considers how individuals respond to certain environmental cues may be more appropriate. Third, a Transactional Model of Placebo Responding in which dispositional characteristics interact with environmental contingencies is presented. Responsiveness may manifest in placebo environments where there is a match between an individual’s biological trait-like response systems and environmental contingencies. This type of model may be useful in both research and clinical settings. Systematic consideration of how different individuals might respond to different placebo environments might facilitate identification of stable individual characteristics predictive of responding. The ability to determine who is responsive to placebo treatments, and in what context, may enable the matching of individual to treatment, thereby maximising the effectiveness of treatment and minimizing possible iatrogenic harm. In the increasingly overtaxed modern healthcare industry non-pharmacological treatment alternatives are of critical importance.
5.1.2 Introduction

The placebo effect, broadly defined as improvements arising from the psychosocial aspect of treatment that are not attributable to artefacts or illness fluctuations, is now recognised as a genuine psychobiological phenomenon [29, 92, 121, 236]. The demonstration of placebo-generated improvements in illness symptomology as well as in neurobiological and physiological outcomes has left little room for doubt [25, 29, 45, 123, 150, 261]. The placebo effect is therefore not a nuisance factor that needs to be controlled in order to determine the efficacy of the ‘real’ treatment, but a powerful mind-body phenomenon associated with improved health outcomes [148].

While the power of the placebo has been established, response rates and effect sizes are hugely variable [50]. While this variability is in part due to study design, outcomes, and the nature of the condition [64, 228], there is also thought to be individual variability in responding. With the use of group averages to detect placebo effects, it is difficult to determine individual response rates within an individual trial [227].

The question of how the placebo effect can be harnessed systematically for the betterment of health has been raised but not yet resolved [21, 193]. Knowledge about an individual’s responsiveness to placebo treatment could guide therapeutic decisions about treatment, including drug and dosage selection [236]. Further, placebo-type interventions may be increasingly relevant for a health industry burdened by psychosomatic complaints and medically unexplained illness [262-265]. Placebo treatments may be the wave of the future but there are questions that remain outstanding.

In order to capitalise on the placebo phenomenon properly, the issue of placebo responsiveness needs to be clarified. Not everyone responds to placebos, and while important situation specific variables such as expectations influence this response [253], whether there are stable individual characteristics associated with responding to placebo treatments is still uncertain [227]. The possible existence of a ‘placebo personality’ therefore remains a gap in our understanding of the placebo effect. Initially discarded, there has been a resurgence of interest in this notion, with recent genetic and neuro-anatomical evidence suggesting that stable traits might predict placebo responding [266]. However, the literature remains somewhat scattered, with no single trait consistently or exclusively related to placebo responsiveness [227, 266]. Not only have a number of overlapping but distinct traits been linked with placebo responses (e.g., optimism [255], extraversion [127], dopamine-related traits [246], and ego resiliency [260]), but other, quite different traits such as
acquiescence [254], suggestibility [135], and absorption [251] have also been associated with greater responses to placebo treatment.

The established links between certain traits and placebo responding, combined with the possibility of therapeutic benefit, indicate that there is merit in continued attempts to identify the ‘placebo responder’; however, it may be that the search would benefit from a slightly different approach. Most prior work has focussed on assessing single traits (such as optimism), or administering higher order personality measures such as the ‘big five’[267]. A number of distinct, and in some cases overlapping traits have been linked to responding (noted above) which decreases certainty that a single higher order personality trait can comprehensively capture the notion of placebo responsiveness. For example, extraversion is a personality dimension that represents multiple related traits [268], and shares considerable overlap with other constructs [127].

The somewhat atheoretical approach in the placebo literature [21] may also be hindering progress. Personality measures, rather than personality theory, appears to be driving research. Measures of higher order traits offer descriptive tools but fall short of explaining how traits influence behaviour [269]. In searching for predictors of behaviour such as placebo responding, descriptive tools may be inadequate.

Given the apparent utility in identifying the ‘placebo responder’ but the inconsistent findings to date, some conceptual clarity and theoretical application may be useful. As a first step it may be useful to consider how findings to date might be organised conceptually. Then, it might be useful to apply personality theory to the question of how personality constructs might predict placebo responding.

5.1.3. A conceptualisation of placebo responsiveness

The overlaps among the traits identified to date suggest that placebo responsiveness could be conceptualised in terms of a two-faceted construct. The term ‘permeability’ has been applied here to describe a perviousness to environmental factors such as treatment rituals and suggestion. Two facets: (i) inward orientation; and (ii) outward orientation are offered to represent the different, but related aspects of placebo responsiveness (Figure 5.1).
Figure 5.1. The umbrella construct ‘permeability’, comprising the two dimensions of inward and outward orientation.

Inward orientation describes a tendency to have an internal focus, or a responsiveness to suggestion as it relates to internal states. Constructs empirically linked with responding that fit within this facet are absorption, suggestibility, and acquiescence. Absorption has been described as indexing the capacity for becoming absorbed in internal experience and disengaging from one’s external environment, and is linked to primary suggestibility via its links with hypnotisability [270]. Both primary suggestibility (hypnotic susceptibility) and secondary (perceptual) suggestibility have been linked with greater placebo response [135, 258]. Greater acquiescence has been associated with a greater placebo responding [254], and outside the placebo field, acquiescence or ‘yea-saying’ has been linked to absorption [271]. Absorption, suggestibility and acquiescence represent a fairly cohesive facet that appears to index a tendency to orient inwards or a capacity to respond to suggestions regarding internal experience.

Outward orientation describes a permeability to external input via an approach behavioural style. Extraversion, dopamine-related traits, optimism, ego resiliency, straightforwardness and altruism can be included in this facet. Extraversion was linked to placebo responding in the context of irritable bowel syndrome [127] and then in subsequent analysis, genetic variants related to dopamine were
associated with this response [249]. In a study that correlated gray matter density with placebo analgesic responses, it was novelty seeking, behavioural drive, and fun seeking (within the dopamine trait) that were associated with placebo responding [246]. Dispositional optimism has been related to greater placebo analgesic responses alone [255] and via an interaction with anxiety reduction [257]. In a recent study placebo analgesic responses were positively predicted by ego resiliency, altruism, and straightforwardness [260]. This cluster of traits reflect a desire to interact with one’s external environment and a tendency to move towards positive and external goals [269]. The grouping of these variables is further supported by empirically demonstrated links among extraversion, positive affect, optimism, fun seeking, drive, and reward sensitivity [272, 273].

While this conceptualisation may be useful in organising findings, it too is only a descriptor tool, and is limited in being able to predict behaviour [269]. In contrast, there are biologically based personality/temperament theories describing how different levels of central nervous system sensitivity generate responses to stimuli, such as avoidance or seeking behaviour [274]. For example, Gray’s [275, 276] temperament theory describes two physiological systems, behavioural inhibition (BIS) and behavioural activation (BAS), that generate predispositions to respond to environmental cues [273]. The BIS has been linked to serotonin pathways, is thought to control the experience of anxiety in response to anxiety-relevant cues, and is sensitive to signs of punishment and novelty [273, 276]. Conversely the BAS is thought to involve dopaminergic pathways and is believed to control appetitive motivation or approach systems [277]. Approach activation generates a movement towards goals and is responsible for the experience of positive feelings when cues for impending reward are presented [273]. The BIS/BAS is structurally consistent with the two-faceted permeability construct and appears to align with the inward and outward facets. Findings to date can be loosely grouped into either of the two facets with inward orientation aligning with the BIS facet and outward orientation aligning with the BAS facet (see Figure 5.1). This alignment suggests it may be useful to conceptualise placebo responsiveness in terms of two facets.

At the core of a stimulus-response model is the environmental stimuli to which an individual responds. Contextual factors are known to be centrally important in the placebo effect [62], [22] and the utility of considering an interaction between disposition and environment has been noted in placebo discourse [260, 266]. However, this interaction has not been thoroughly investigated [266], and a model incorporating such an interaction has not yet been offered. A model of placebo
responsiveness that considers the interaction between dispositional characteristics and environmental cues may provide an integral piece of the placebo ‘puzzle’.

5.1.4. A Transactional Model of Placebo Responding (TMPR)

Transactional models attempt to explain behaviour by considering the dynamic relationship between a person and their environment. Perhaps due to Engel's seminal biopsychosocial model [278], they are now widely used in psychology and medicine, and have been applied to areas such as in psychopathology [279], stress responses [280] and decision-making [281]. A Transactional Model of Placebo Responding is presented here, depicting the interaction between dispositional and environmental variables (Figure 5.2). Responsiveness may manifest in placebo environments where there is a match between an individual's biological trait-like response systems and environmental contingencies. For example, persons motivated by serotonin-related harm-avoidant systems (inward orientation) may respond to authoritative instruction in non-threatening contexts, and where instructions or measures focus on the individual's internal state. Conversely those with ‘approach’ tendencies (outwardly oriented) may differentially respond to external cues or goals such as a friendly practitioner, or exciting and novel treatments (Figure 5.2).

![Transactional Model of Placebo Responding](image)

*Figure 5.2. Transactional Model of Placebo Responding in which the two facets of permeability (inward/outward) represent predispositions to respond to environmental cues, with potentially appropriate cues and possible pathways described.*
There is some empirical support for the importance of the disposition-environment interaction. For example, it has been suggested that the link between dispositional optimism and placebo responding in pain paradigms may arise only because the situational cues present in placebo analgesia manipulations match the positively valenced nature of optimism [282]. Similarly, a study found that extraversion only predicted placebo responding when treatment was delivered by a caring and empathic practitioner [127]. Empathic concern was only associated with placebo analgesic responses in the condition that included a confederate undergoing painful stimuli [95].

A match between disposition and environmental cues may be vital for generating placebo responses, and the non-systematic presence of appropriate cues for either facet may help explain some of the inconsistencies in the extant literature. That is, when there is not a match between the type of individual and the nature of the contextual cues, responding may not arise. Further, a particular placebo paradigm may elicit responses from a certain individual but that trait may not have been measured and thus no personality-responding link is found. Equally, the reason that most evidence implies an outwardly oriented responder (Figure 5.1) may reflect the fact that most placebo research has been conducted within pain or related settings. Environmental contingencies available in pain-related paradigms, such as interactions with empathic practitioners, positively valenced goals or externally oriented cues (e.g., suggestion regarding the reduction of noxious stimuli) may be better suited to outwardly oriented individuals. More research is needed to test this model, with systematic manipulation of environmental cues measured against personality traits.

5.1.5. Clinical applications

The ability to determine who is responsive to placebo treatments, and in what context, may facilitate effective treatment design by matching treatment to individuals. Both responders and non-responders could be considered in deciding on the nature or dosage of treatment. It has been suggested that such an approach could maximise the possible effectiveness of treatment and minimize possible iatrogenic harm [236]. Further, since the placebo effect is essentially the effect of the therapeutic context [62], there is a placebo component to traditional (pharmaceutical) treatments [236], and there are indications that there are dispositional variables associated with being more responsive to both sham
and ‘real’ treatment [251]. While some individuals may experience adverse effects from inert treatments [283], whether such individuals fit into this model is a question for further research.

By using this transactional model, health practitioners could maximise the placebo component of any treatment or increase the likelihood of responding to treatment by tailoring their approach based on how certain individuals respond to contextual treatment cues. For example, a treatment could be presented either to suit the outwardly oriented or BAS sensitive individual, or the inwardly oriented BIS sensitive individual by adjusting the presence or absence of novelty or a focus on internal or external outcomes.

Placebo responsiveness could also be applied to the treatment of illnesses that are medically unexplained or heavily influenced by psychosomatic factors. In the absence of known organic pathology, a non-pharmaceutical treatment may be a better approach. For example, the origins and mechanisms of Irritable bowel syndrome (IBS) are not yet properly understood, and worldwide prevalence rates are up to 25% [284, 285]. IBS has been clearly shown to be responsive to placebo treatments [46, 126, 127], even when patients are told they are receiving a placebo treatment [126]. Thus there is utility in identifying those who are placebo responsive, and then capitalising on placebo mechanisms to effect better treatment of such a condition.

In summary, the permeability conceptualisation offered here, together with the Transactional Model that considers predispositions to respond to particular environmental contingencies, may facilitate predicting placebo responding. The development of such a model may not only benefit scientific research endeavours, but may also provide a useful clinical tool [226]. Health practitioners may be able to enhance therapeutic effects by appropriately structuring their interventions based on patients’ dispositional tendencies. The clinical approach could be tailored to minimize the risk of undertreatment or iatrogenic effects and therapeutic style could be adjusted to maximise individual health outcomes. Illnesses without clear pathogenesis are a burden on the modern healthcare system [265], and alternatives that are not based on pharmacological treatment of physiological pathology are urgently needed.
The preceding chapter presented a Transactional Model of Placebo Responding (TMPR) in which placebo responsiveness is characterised by the two facets of inward and outward orientation. Persons characterised by either facet have the potential to respond to placebo treatments but may do so in the presence of different environmental stimuli, with placebo responding resulting from the transaction between the individual’s dispositional style and the specific cues in their environment.

When organising prior findings around these two facets (Figure 5.1), it becomes apparent that there is more evidence for the outwardly oriented responder. However, rather than an indication that this ‘type’ is a better characterisation of responsiveness per se, it may simply reflect the fact that most placebo research has been conducted in pain-related paradigms (Table 4.2). As suggested in Chapter 5, the two facets are thought to be responsive to different environmental cues and the particular cues available in pain paradigms may preferentially elicit responses from the outwardly oriented individual.

The focus of the extant literature in experimental pain paradigms represents the second limitation of the placebo personality literature. To gain a more comprehensive understanding of placebo responsiveness as a dispositional style, more research is needed to investigate personality predictors in other settings. To address this limitation, two papers documenting personality predictors in the context of recovery from psychosocial stressors (6.1) and inflammatory skin reactions (6.3) are presented next. Note that the findings presented in these two papers are derived from the two experimental studies described earlier, which were also the basis for the two papers presented in Chapter 3.1 and Chapter 3.3 documenting placebo effects in non-pain contexts (see Figure 1.1). The data overlaps pertain to the sample and description of methods only.

In considering these two reports, it is important to note that both were constructed with the aim of identifying personality predictors of placebo responding in non-pain contexts, rather than as direct tests of the TMPR presented in the previous chapter. Given that the optimal operationalisations of the model were yet to be determined, a measurement approach that traded off breadth against the issues associated with power and practicality was taken.

In selecting specific measures the BIS/BAS [273], a psychometric proxy for Gray’s approach/avoid model, was chosen as a possible operationalisation of both the inward (BIS) and
outward (BAS) facets. To increase content validity, measures of optimism, empathy, and extraversion were included in assessment of the outward orientation facet (note, dopamine-related traits are captured within the ‘BAS’ measure). The inclusion of these measures also facilitates comparisons with prior research.

To further represent inward orientation, the traits of absorption and neuroticism were selected. The tendency to become absorbed in internal experience is, at face value, a good representation of an inwardly oriented type, and trait absorption has been found to overlap with suggestibility, hypnotisability and acquiescence [270, 271]. Thus, absorption potentially captures an aspect of ‘inward orientation’ that is not represented by the anxiety-related BIS scale. Neuroticism was selected as an additional measure because the inwardly oriented individual is an anxiety-prone type with an internal focus and early work suggested a neurotic anxious type might best typify responsiveness [286].
6.1. Personality predictors of placebo responding in the context of stress recovery


6.1.1. Abstract

**Aim.** To identify personality traits related to placebo responding outside the context of pain. **Methods.** Sixty three healthy volunteers completed the study. Personality traits were measured online one week prior to a laboratory session in which two psychosocial stress tests were administered. Prior to the second test, the placebo group received an intranasal spray of ‘serotonin’ (placebo) with the suggestion that it would enhance recovery. Subjective stress, heart rate and heart rate variability were measured. Self-reported and physiological responses to the placebo suggestion were assessed against personality variables. **Results.** Placebo effects were demonstrated in both self-reported and physiological stress metrics. Lower optimism and less empathic concern predicted greater perceived benefits from the placebo treatment; and lower drive, fun, and sensation seeking were related to a greater physiological response to the manipulation. Multivariate analyses revealed lower optimism and behavioural drive to be predictive of responding to the placebo manipulation. **Conclusion.** Findings are in contrast with prior work in pain paradigms which found higher levels of the same traits to be related to greater placebo analgesic responses. A cluster of traits characterised by behavioural drive, extraversion, optimism and novelty or fun seeking appears to be germane to placebo responsiveness, but contextual stimuli may generate different patterns of responding. A new conceptualisation of placebo responsiveness may be useful. Rather than a ‘placebo personality’ it may be that responsiveness is better typified by a two faceted transactional model, in which different personality facets respond to different contextual contingencies.
6.1.2. Introduction

There is now a vast literature documenting the placebo effect. While considerable progress has been made towards understanding this phenomenon [29], a question that remains unresolved is whether we can identify reliable personality predictors of the placebo response [227]. Recent evidence suggests that responsiveness might be typified by a cluster of positively valenced, reward related and socially oriented traits. Optimism [255, 257, 282], empathy [95], extraversion [127], ‘dopamine-related’ traits [246], ego resilience, altruism, straight forwardness and low hostility [260] have been linked to greater responding. These traits are cohesive and share conceptual and empirical links [272, 273].

However, most placebo research has been conducted within pain or related contexts [136] and the link between these traits and responding may be not be generalisable. Particular environmental contingencies are available in pain paradigms. Interactions with empathic practitioners, positively valenced goals, and externally oriented cues may be optimally suited to facilitating responding in this social, positive, and reward responsive personality type. For example, extraversion predicted placebo induced improvements in irritable bowel syndrome symptoms only in the presence of an empathic practitioner [127]. Empathic concern was only related to placebo analgesic responses in a social learning condition that involved a confederate [95], and the link between optimism and responding may only eventuate in positively valenced contexts [256, 287].

Thus, it is not entirely clear whether the aforementioned ‘type’ represents a generic placebo responder or just one type of responsiveness that is exhibited in pain paradigms. There may be other traits associated with placebo responsiveness in other contexts. For example, research in non-pain paradigms has found other traits, such as absorption [251], acquiescence [254], and suggestibility [135], to be associated with greater responding. A broadening of context beyond placebo analgesia, with a concomitant broadening of measurement is needed to fully investigate the possibility of other placebo responsive types.

The purpose of this study was to identify personality traits related to placebo responding outside the context of pain. Personality was assessed via an online questionnaire 1-2 weeks prior to an experimental session in which two psychosocial stress tests were administered. Prior to the second test, placebo ‘serotonin’ was administered via an intranasal spray with the suggestion that it would enhance recovery. Self-reported and physiological indicators of stress were assessed. A control group
underwent the same procedures other than the administration of the intranasal spray and the accompanying suggestion.

6.1.3. Methods

Participants

A sample of 63 healthy volunteers was recruited via invitations posted on the University of Auckland intranet and social media sites (Figure 6.1). No course credit was available for participation. To be eligible, participants had to be English speakers, have no recent psychopathology, chronic medical or heart conditions, and, if female, not be pregnant. Those eligible to take part were sent consent forms and then a link to an online personality questionnaire. After questionnaire completion participants were scheduled for a 75 minute laboratory session.

![Flow chart of study recruitment, enrolment, participation including any necessary exclusions.](chart.png)

*Figure 6.1. Flow chart of study recruitment, enrolment, participation including any necessary exclusions.*
**Blinding and randomization**

Participants were block randomized into placebo or control conditions by the researcher (M.D) after the initial introductory overview, to avoid knowledge of group allocation affecting Phase I procedures (Figure 6.2). The researcher also delivered the placebo manipulation. The research assistant (RA) was blind to group and so could neutrally administer both stress tests.

6.1.4. Experimental Procedure

To begin, the researcher described procedures and reiterated the deceptive cover story (investigating the interaction between serotonin, stress recovery, and psychological factors). The researcher then left the lab and the RA carried out all Phase I procedures (Figure 6.2) starting with baseline measures (Base1) of heart rate (HR), heart rate variability (HRV), and stress (S1). The RA then administered the first stress test, a 5 minute mental arithmetic test involving sequential subtraction adapted from a previous study [165]. Participants were asked sequentially to subtract 163 from 8500 as quickly as possible. Participants could not progress until they gave the correct answer. Reported stress was measured immediately afterwards (S2), and then a 5 minute recovery period commenced (Recover1). After this period stress was again assessed (S3), marking the end of Phase I and the start of a 5 minute break. In Phase I all participants underwent the same procedures.

![Figure 6.2. Experimental protocol for Phase I and Phase II with tasks (unbroken lines) and measures (dashed lines). Shaded boxes indicate tasks carried out by the researcher (all others administered by RA). BQ = baseline questionnaire; S1 – S6 = self-reported stress measures.](image-url)
Phase II commenced with measures of stress (S4), HR, and HRV (Base2). The researcher then replaced the RA and remained in the lab for the duration of Phase II. Participants were told whether they were in the ‘serotonin’ (placebo) group or the control group and shown a ~2.5 minute video. For the control group this emphasised the importance of controls in experimental trials. The placebo group was told that they would receive an intranasal dose of serotonin immediately before and after a second stress test which would enhance their recovery from the stressor.

‘Serotonin is a neurotransmitter… involved in regulating your stress response…. specifically in your recovery from stress….It will enhance your recovery from the stressor by reducing your heart rate … make you feel less stressed…’

The researcher then administered the ‘serotonin’ (5% saline solution) to the placebo group with one spray in each nostril. It was left to ‘absorb into the system’ for 30 seconds. Control participants were advised that they would undergo a second stress test. They received no spray to avoid the possibility of this treatment ritual affecting responses [166].

The RA then re-entered the room and administered the second stress test. Participants were told the second test was the same as the first except for the starting number (8600) and subtraction number (177). The researcher remained in the room behind a screen in an attempt to counteract habituation to the test without deviating too much from Phase I procedures. The RA measured stress (S5) before leaving the room. Placebo group participants received a top up dose of ‘serotonin’ (same procedure) to ‘enhance their recovery during the five minute recovery period’ (Recover2). The control group received nothing. After one final stress measure (S6) the placebo group were asked an extra question about the effectiveness of the serotonin. All participants were given a $20 voucher and thanked for their time.

6.1.5. Measures

Pre-experiment assessment of dispositional constructs

Approximately 1-2 weeks before the experimental session participants completed an online personality survey. Temporal separation of the administration of the questionnaire from experimental manipulations reduces method biases [288].
EPQ-R Short Version [289]: extraversion and neuroticism subscales. For each subscale participants rated how much they agreed with 12 statements using a 1 ('I agree a lot') to 5 ('I disagree a lot') scale. Reliability for both scales was good (extraversion $\alpha = .92$, neuroticism $\alpha = .84$). Both scales were coded so that higher aggregate scores indicated higher levels of each trait.

BIS / BAS [273]: measures individuals’ tendencies for behavioural inhibition (BIS) or behavioural activation (BAS) systems [275, 276]. Participants rate agreement with 20 statements from: 1 (‘strongly agree’) to 4 (‘strongly disagree’). The BIS facet is measured by one 7 item subscale assessing sensitivity to anxiety relevant stimuli ($\alpha = .79$). The BAS facet is measured by three scales with four to five items in each: ‘Fun’ indexes novelty and fun seeking ($\alpha = .77$), ‘Drive’ indexes a ‘go getter’ approach ($\alpha = .86$), and ‘Reward’ assesses reward sensitivity ($\alpha = .87$). All subscales were coded so that higher scores indicated higher levels of each facet.

Life Orientation Test Revised [290]: assesses dispositional optimism via a 10 item scale with four filler items. Participants rated each item on a 1 (‘agree a lot’) to 5 (‘disagree a lot’) scale. The scale was coded so that higher scores indicated higher levels of optimism ($\alpha = .78$).

Modified Tellegen Absorption Scale [291]: adapted from the original Tellegen Absorption Scale [292], measures the extent to which an individual fully commits attentional resources. The scale was modified from a Yes/No format to a Likert scale [291]. Participants rated how frequently statements were true of their experience from 0 = ‘Never’ to 4 = ‘Very Often’. The scale was coded so that higher scores indicated higher levels of absorption ($\alpha = .93$).

The Interpersonal Reactivity Index [293]: a 28 item measure indexing four aspects of empathy via four subscales. Participants rate each item on a five point scale (‘A = ‘does not describe me well’ to E = ‘describes me very well’). (1) Distress: assesses emotional discomfort and unease in crises ($\alpha = .79$); (2) Empathic: measures the concern one has for others ($\alpha = .78$); (3) Fantasy: measures the tendency to get involved in characters in books and movies ($\alpha = .73$); and (4) Perspect: measures how much
individuals consider another’s point of view ($\alpha = .76$). All subscales were coded so that higher scores indicated higher levels of each facet.

**Experimental self-report measures**

*Baseline Questionnaire (BQ)*

A one page form assessed demographics (age, sex, ethnicity), and self-reported health behaviours (BMI, smoking, caffeine and alcohol intake, and activity levels).

**Subjective stress**

Participants rated stress using a 5 item scale developed for this study. Participants indicated on an 8 point scale (1 = ‘not at all’, 8 = ‘extremely’) how (1) ‘stressed’ they were, (2) how much they felt a physiological stress response (i.e., an elevated heart rate), (3) how tense, (4) anxious, and (5) strained, they felt. All stress assessments (S1 to S6) had good internal consistency ($\alpha = .85$ to .95).

**Self-reported effects of the ‘serotonin’**

Placebo group participants were asked to rate the ‘extent to which the serotonin enhanced recovery from the stress test’ from 1 (‘not at all’) to 8 (‘extremely’) as an additional item in the final stress measure.

**Experimental physiological measures**

*Heart rate (HR) and Heart Rate Variability (HRV)*

HR and HRV were measured continuously throughout the experiment with the non-invasive RS800 Polar HRV wristwatch and chest band. HR provides an indication of physiological arousal and mean HR in beats per minute (bpm) was used in analysis. HRV describes the beat to beat variation in heart rate, with higher HRV indicating better cardiac regulation [169]. High frequency (HF) spectral power HRV is thought to measure the amount of vagal input regulating sympathetic activity [171], which indexes recovery from stressors [120]. Artefact correction was carried out in Kubois HRV 2.0 (Biosignal Analysis and Medical Imaging Group, Kuopio, FINLAND), which has a sampling rate of 1000 Hertz [171]. The HRV high frequency (HF) data was positively skewed and was natural log transformed. The HRV measure used in analysis was High Frequency ms$^2$ autoregression spectrum.
6.1.6. Statistical Analysis

Between group analyses were carried out to check for baseline differences in demographics and outcome variables. Repeated measures ANOVAs were used to test for placebo effects. To test for links between personality traits and placebo responses, Pearson’s Product Moment correlations or Spearman’s rho tests were conducted with the data stratified by group. R to Z transformations were then conducted to test the difference in placebo and control group coefficients. Finally, three stage forced entry multiple regressions were conducted. Group was entered as step one, personality entered as step two, and then group by personality interaction terms was entered for those traits significantly associated with outcome variables in the placebo group. Variables were centred prior to entry into the model.

Several individual data points were not available for some HR and HRV variables and treated as missing data. The S5 stress measure was missing for two participants (one from each group) due to procedural errors. Two participants were excluded prior to hypothesis testing as they were unaffected by the stress test (i.e., they reported no stress after the Phase1 stress test).

6.1.7. Results

Preliminary analyses (Table 6.1)

Sample demographics are reported in Table 6.1. There were no baseline differences in demographics, health behaviours, and pre manipulation outcome measures (all $p > .05$). For personality, a MANOVA revealed no main effect of group ($\lambda = .75, F(13,46) = 1.16, p = .34$). The placebo group on average had a later experimental session (Table 6.1). Given that circadian fluctuations and changes in energy could affect outcome measures, ‘time of session’ was added as a covariate in analyses. Gender can affect responses to stress [176]; however, with no sex differences in the outcomes it was not added as a covariate.
Table 6.1.
Results of baseline between group tests (sex, ethnicity, age, health behaviours and session time), and tests for placebo effects (repeated measures ANOVAs) in reported stress, HR and HRV, with means, standard deviations, degrees of freedom, test statistics, significance values and effect sizes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 31)</th>
<th>Placebo (n = 29)</th>
<th>Χ²</th>
<th>df</th>
<th>p</th>
<th>φ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% Female)</td>
<td>21/31 (68%)</td>
<td>20/29 (69%)</td>
<td>.01</td>
<td>1</td>
<td>.57</td>
<td>.002</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>16/31 (52%)</td>
<td>14/29 (48%)</td>
<td>.07</td>
<td>1</td>
<td>.50</td>
<td>.004</td>
</tr>
<tr>
<td>Age ( M (SD) )</td>
<td>20.84 (2.62)</td>
<td>20.48 (2.50)</td>
<td>.54</td>
<td>58</td>
<td>.59</td>
<td>.14</td>
</tr>
<tr>
<td>BMI ( M (SD) )</td>
<td>22.42 (2.90)</td>
<td>22.08 (3.16)</td>
<td>.44</td>
<td>58</td>
<td>.66</td>
<td>.11</td>
</tr>
<tr>
<td>Self-reported health</td>
<td>3.77 (.71)</td>
<td>3.90 (.67)</td>
<td>.68</td>
<td>58</td>
<td>.50</td>
<td>-.19</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>2.23 (1.26)</td>
<td>2.28 (1.13)</td>
<td>.16</td>
<td>58</td>
<td>.87</td>
<td>-.04</td>
</tr>
<tr>
<td>Caffeine intake</td>
<td>3.32 (1.01)</td>
<td>2.93 (1.19)</td>
<td>1.4</td>
<td>58</td>
<td>.18</td>
<td>.36</td>
</tr>
<tr>
<td>Activity Level</td>
<td>4.35 (1.17)</td>
<td>4.17 (1.42)</td>
<td>.55</td>
<td>58</td>
<td>.59</td>
<td>.14</td>
</tr>
<tr>
<td>Session time (24 hour)</td>
<td>11.25 (2.14)</td>
<td>12.50 (2.37)</td>
<td>-2.15</td>
<td>58</td>
<td>.04</td>
<td>-.56</td>
</tr>
</tbody>
</table>

Placebo Effects

<table>
<thead>
<tr>
<th>S2 (start of Recover1)</th>
<th>23.42 (1.36)</th>
<th>20.33 (11.68)</th>
<th>F(1,51) = 13.10</th>
<th>&lt; .01</th>
<th>.19</th>
</tr>
</thead>
<tbody>
<tr>
<td>S5 (start of Recover2)</td>
<td>23.45 (1.33)</td>
<td>14.27 (8.72)</td>
<td>F(1,51) = 2.65</td>
<td>.11</td>
<td>.05</td>
</tr>
<tr>
<td>HR Recover1</td>
<td>77.09 (10.18)</td>
<td>80.12 (12.96)</td>
<td>F(1,51) = 5.81</td>
<td>.02</td>
<td>.10</td>
</tr>
<tr>
<td>HR Recover2</td>
<td>75.13 (9.40)</td>
<td>75.55 (10.31)</td>
<td>F(1,51) = 2.65</td>
<td>.11</td>
<td>.05</td>
</tr>
<tr>
<td>HRV Recover1</td>
<td>6.68 (1.32)</td>
<td>6.29 (.93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRV Recover2</td>
<td>6.65 (1.12)</td>
<td>6.81 (.83)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Assessment of Placebo Effects

The verbal manipulation suggested enhanced recovery from the stressor after receipt of the 'serotonin'. Changes in reported stress, HR and HRV from Recover1 to Recover2 were assessed via three 2 (Group) by 2 (Time) repeated measures ANOVAs. Placebo effects were demonstrated in reported stress and in HRV. Compared to controls, the placebo group reported a greater reduction in stress and had a greater increase in HRV from Recover1 to Recover2. There was a non-significant trend for the placebo group to have a greater reduction in HR (Table 6.1).

Stress test scores and perceived difficulty

The placebo group perceived the second stress test to be less difficult than the first (M = -1.31, SD = 1.20), and this reduction trended towards being greater (t(1,57) = 1.68, p = .10) than the control group's reduction in perceived difficulty (M = -.80, SD = 1.13). Nevertheless, there was no difference
between the groups in performance on the stress test at either time point \((p > .05)\). In the control group only, higher BAS reward was related to lower stress test scores at Time 1 \((r = -.55, p < .01)\) and at time2 \((r = -.44, p = .02)\). In the placebo group there was one marginal relationship between higher extraversion and lower perceived difficulty of the second stress test \((r = -.36, p = .06)\).

**Personality and self-reported ‘serotonin’ effects**

Placebo group participants were asked to rate how effective the serotonin was in enhancing their recovery from the stressor. Correlational analysis revealed that lower optimism and empathic concern were associated with greater perceived effects of the ‘serotonin’. There were also trends for lower extraversion and BAS fun to be associated with the ‘serotonin’ being seen as more effective, indicating that being introverted and novelty aversive may be associated with experiencing more benefit from the treatment (Table 6.2).

**Personality and placebo responses in self-reported stress**

Before analyses, an average of the two post placebo manipulation subjective stress measures was calculated \((s5 \text{ and } s6; r = .66, p < .001)\) for use in analysis, along with the reported change in stress from the start of Recover1 to the start of Recover2 (stress change s2 to s5). There were no relationships in the placebo group across any of the reported stress variables (Table 6.2); however, in the control group there were several significant relationships. More drive and greater absorption were associated with greater stress in phase II. Higher extraversion, empathic fantasy, optimism, BAS reward, and sensation seeking were associated with a greater reduction in stress over time.

**Personality and physiological placebo responses**

In the placebo group, higher HRV in Recover2 was associated with lower BAS drive and higher absorption, indicating that these traits were related to a greater response to the manipulation. R to Z tests revealed that the coefficient for Recover2 HRV and drive in the placebo group was significantly different to the control group, whereas for absorption this difference was marginal (Table 6.2). Change in HR was related positively to BAS fun and sensation seeking, and negatively to neuroticism. Being more neurotic, novelty aversive, and sensation avoidant were related to a greater reduction in HR, which was consistent with the verbal suggestion. R to Z tests revealed that the coefficient between fun
and change in HR differed between placebo and control groups. The differences for sensation seeking and neuroticism were marginal (Table 6.2). No variables were related to mean HR in Recover2 or the change in HRV in the placebo group. In controls, being more extraverted was related to higher HRV in recover2 and having greater empathic concern was related to a greater drop in HR over time (Table 6.2).

**Multiple regressions**

Forced entry regressions were carried out and results are listed in Table 6.3.

In predicting self-reported effects of the serotonin, empathic concern and optimism were force entered in one step. The model was significant (Table 6.3) explaining 30% of the variance. Optimism was the only individual predictor with lower optimism predicting greater reported serotonin effects.

In predicting change in HR, the group by personality product term trended towards significance ($p = .09$). Note that interactions tested via this analysis may have low power and some have suggested alpha might be set more generously at $p < .10$ [294]. There were also trends for group by sensation seeking, and group by neuroticism to predict the change in HR (Table 6.3). Those lower in sensation seeking and higher in neuroticism tended to have a greater reduction in HR after they received the placebo.

In predicting HRV in Recover2, the group by personality interaction was marginally significant ($p = .05$), explaining 16% of the variance in HRV in Recover2 (Table 6.3). The group by drive product term was a significant individual predictor (Table 6.3). Lower drive predicted higher HRV, indicating a greater regulatory response.
<table>
<thead>
<tr>
<th>Trait variable</th>
<th>Sero-tonin effects (r)</th>
<th>Average stress s5 and s6 (\rho)</th>
<th>Change in reported stress s5-s2 (\rho)</th>
<th>HF HRV Recover2 (\rho)</th>
<th>Change in HF HRV r2-r1 (\rho)</th>
<th>HR Recover2 (\rho)</th>
<th>Change in HR r2-r1 (\rho)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pbo (n=29)</td>
<td>Ctrl (n=30)</td>
<td>Pbo (n=29)</td>
<td>z</td>
<td>Ctrl (n=28)</td>
<td>Pbo (n=26)</td>
<td>z</td>
</tr>
<tr>
<td>Reward</td>
<td>.01</td>
<td>.04</td>
<td>-.35(t)</td>
<td>1.48(t)</td>
<td>-.14</td>
<td>-.26</td>
<td>.43</td>
</tr>
<tr>
<td>Drive</td>
<td>&lt;.01</td>
<td>.37(\ast)</td>
<td>.13</td>
<td>.94</td>
<td>.11</td>
<td>-.08</td>
<td>.66</td>
</tr>
<tr>
<td>Fun</td>
<td>-.32(t)</td>
<td>-.15</td>
<td>-.18</td>
<td>.11</td>
<td>-.36(t)</td>
<td>.10</td>
<td>-.16(t)</td>
</tr>
<tr>
<td>BIS</td>
<td>&lt;.01</td>
<td>.20</td>
<td>-.03</td>
<td>.85</td>
<td>.08</td>
<td>-.02</td>
<td>.35</td>
</tr>
<tr>
<td>Extraversion</td>
<td>-.37(t)</td>
<td>-.12</td>
<td>-.18</td>
<td>.22</td>
<td>-.42(\ast)</td>
<td>-.15</td>
<td>-.10</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>.24</td>
<td>.21</td>
<td>.19</td>
<td>.08</td>
<td>.09</td>
<td>-.10</td>
<td>.66</td>
</tr>
<tr>
<td>Optimism</td>
<td>-.53(**)</td>
<td>-.34(\ast)</td>
<td>-.01</td>
<td>-.138(t)</td>
<td>-.43(\ast)</td>
<td>.16</td>
<td>-2.15(\ast)</td>
</tr>
<tr>
<td>Sensation Seeker</td>
<td>-.23</td>
<td>-.46(\ast)</td>
<td>.06</td>
<td>-.203(\ast)</td>
<td>-.43(\ast)</td>
<td>.15</td>
<td>-.21(\ast)</td>
</tr>
<tr>
<td>Absorption</td>
<td>-.21</td>
<td>.40(\ast)</td>
<td>.19</td>
<td>.84</td>
<td>.08</td>
<td>-.01</td>
<td>.28</td>
</tr>
<tr>
<td>Perspective</td>
<td>-.13</td>
<td>.03</td>
<td>-.16</td>
<td>.70</td>
<td>-.11</td>
<td>-.11</td>
<td>0</td>
</tr>
<tr>
<td>Fantasy</td>
<td>-.13</td>
<td>.03</td>
<td>-.18</td>
<td>-.55</td>
<td>-.47(**)</td>
<td>-.15</td>
<td>-1.24</td>
</tr>
<tr>
<td>Empathic</td>
<td>-.38(\ast)</td>
<td>.08</td>
<td>-.07</td>
<td>.55</td>
<td>-.14</td>
<td>.07</td>
<td>-.73</td>
</tr>
<tr>
<td>Distress</td>
<td>.04</td>
<td>.18</td>
<td>.26</td>
<td>-.31</td>
<td>.06</td>
<td>-.01</td>
<td>.21</td>
</tr>
</tbody>
</table>

**\(p < .001\)  
\(\ast\) \(p < .05\)  
\(t\) \(p = .05 \text{ to } .10\)
Table 6.3.
Results from a one-step forced entry multiple regression for self-reported serotonin effects, and two three-stage forced entry multiple regressions for change in HR and Recover2 HRV.

<table>
<thead>
<tr>
<th></th>
<th>Self-reported effects</th>
<th>Change in HR</th>
<th>HRV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B</strong></td>
<td><strong>SE</strong></td>
<td><strong>Beta</strong></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td><strong>Step 1 - Group</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Model</strong></td>
<td>R = .21, R² = .05, F(1,52) = 2.50</td>
<td>R = .08, R² = .007, F(1,52) = .35</td>
<td></td>
</tr>
<tr>
<td><strong>Step 2 – Personality</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Group</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Empathic concern</td>
<td>-1.41</td>
<td>.70</td>
<td>-.14</td>
</tr>
<tr>
<td>Optimism</td>
<td>-.50</td>
<td>.60</td>
<td>-.46</td>
</tr>
<tr>
<td>Fun</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sensation seeking</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Absorption</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Drive</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Model</strong></td>
<td>R = .54, R² = .30, F(2,26) = 5.45, p = .01</td>
<td>R = .55, R² = .30, R²Δ=.25, F(4,49) = 2.50**, FΔ(3,49) = 5.91**</td>
<td>R = .23, R² = .05, p = .32 R²Δ=.04, F(3,50) = .89, FΔ(2,50) = 1.16</td>
</tr>
<tr>
<td><strong>Step 3 – Interaction</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Group*fun</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Group*neuroticism</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Group*sensation</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Group*absorption</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Group*drive</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Model</strong></td>
<td>R = .63, R² = .39, R²Δ=.09, F(7,46) = 4.23**, FΔ(3,46) = 2.33t</td>
<td>R = .40, R² = .16, R²Δ=.11, F(5,48) = 1.86, FΔ(2,48) = 3.19*</td>
<td></td>
</tr>
</tbody>
</table>

**p < .001, *p < .05, ip = .05 to .10**
6.1.8. Discussion

The purpose of this study was to investigate the personality traits associated with placebo responding outside the pain context. Within an experimental stress protocol, the placebo manipulation enhanced subjective and physiological recovery from a psychosocial stress test. Several personality traits were found to be related to placebo responses. Lower optimism and less empathic concern were related to greater perceived benefit from the placebo treatment. Less behavioural drive, lower fun and sensation seeking, but higher absorption and neuroticism were related to greater physiological (HR, and HRV) placebo responses. Multiple regressions revealed that lower optimism and behavioural drive were both predictive of greater responses to the placebo manipulation. Below, these findings are interpreted in light of prior placebo research as well as personality theory.

In prior work using pain related paradigms, a cohesive cluster of traits have been fairly consistently linked to greater placebo responding. Higher levels of optimism [255, 257], empathic concern [95], extraversion [127], fun, drive, and novelty seeking [246], have been related to greater placebo analgesic responses. In the current study however, it was lower optimism and less empathic concern that predicted the experience of greater benefit from the placebo treatment. Extraversion and fun seeking also trended in the same direction. Further, lower drive, fun, and sensation seeking, and higher neuroticism were related to greater physiological placebo responses. Although these data are preliminary and in need of replication, the overall pattern of results clearly contrasts with the prior work described above. The fact that a distinct and near-opposite pattern of findings within the same cluster of personality constructs predicting responding in a non-pain context suggests that it might be worth considering placebo responsiveness from a slightly different perspective.

More work is clearly needed outside pain contexts; however, it may be that a cluster of traits is relevant to placebo responsiveness, but that different patterns of responding emerge depending on the context. Context is known to be an important component of placebo effects [22]. To this, the current report adds the suggestion that the generation of a placebo response may reflect interactions between dispositional traits and contextual stimuli in the placebo environment. The importance of disposition environment interactions in placebo responding has been noted in placebo discourse [260, 266], and there is some support for this observation. For example, extraversion was only related to responding in an augmented treatment condition delivered by an empathic practitioner [127], and empathic concern was only related to placebo analgesic responses in a social observational condition in which a confederate underwent painful stimuli [95]. Further, higher optimism was related to placebo
responses when the manipulation was positively valenced, but when the valence was negative, lower optimism was associated with responding to the placebo [287]. Despite these findings, a theoretical model of placebo responsiveness that incorporates disposition environment interactions has not yet been offered.

Two factor personality theories are used to explain how different nervous system sensitivities generate different behaviours in response to environmental stimuli [273, 274] and thus represent a disposition environment model. Gray’s behavioural inhibition (BIS) and behavioural activation (BAS) theory describes two physiological systems that generate predispositions to respond to environmental cues [275, 276]. The BIS generates ‘avoid’ behaviour and is sensitive to anxiety cues [273, 276], while the BAS generates appetitive ‘approach’ behaviour in response to positive reward cues [273, 277]. BIS/BAS scores, which measure these ‘avoid’ or ‘approach’ tendencies, were linked to responding in the current study as well as in prior work (above). Thus, there is an indication that a two factor model such as this may be relevant in the context of placebo responsiveness.

The application of a two factor transactional model facilitates interpretation of the current study findings in light of prior work, which is difficult otherwise. Findings in the extant literature linking personality traits to placebo responding can be broadly grouped into the two faceted BIS/BAS model. The bulk of findings arising from pain paradigms denote high BAS, low BIS sensitive individuals responding to placebos. Optimism, extraversion, fun, drive, empathy, ego resiliency, altruism and novelty or sensation seeking can all be described as BAS facets, mediated by approach systems. As noted earlier, these traits are cohesive, with empirically demonstrated links to placebo responsiveness (above), as well as to one other [272].

Research in non-pain paradigms however, has linked traits that reflect aspects of the BIS facet to responding. Greater absorption was related to greater symptom reduction after a sham treatment in multiple sclerosis patients [251]. Highly suggestible participants had a greater response to a sham bronchoconstriction manipulation [135], and higher acquiescence was related to greater placebo responses in anxiety and depression patients [254]. In the current context of stress recovery, it was low BAS, high BIS individuals that responded to the manipulation. The BIS facet is a neuroticism like construct [295] and there are conceptual links between absorption, suggestibility and acquiescence [270, 271, 296-298]. Thus, there is a second, relatively cohesive cluster of traits which have also been linked to placebo responding in different contexts.
Findings in the extant literature linking personality traits to placebo responding can be broadly grouped into this two faceted model, and it appears that different aspects of a ‘placebo personality’ may respond to different types of cues in placebo contexts. While the literature above was grouped into pain versus non-pain contexts, it is important to clarify that this does not suggest that a distinction should be made between those who respond to placebo analgesia contexts versus those who respond to non-analgesia paradigms. Rather, it may be underlying differences in the salient cues that generate different patterns of responding. The BIS/BAS model could be used as a theoretical model to investigate responding to approach versus avoidance cues in multiple placebo contexts.

It is worth commenting on the trend for an inverse relationship between extraversion and perceived difficulty of the second stress test in the placebo group. It may be that for those more oriented towards social cues, the ‘stress reduction’ suggestion delivered by the experimenter had the effect of reducing the noxiousness of the stress challenge. Finally, while lower levels of empathic concern, extraversion, fun, optimism, sensation seeking were associated with greater placebo responding, higher levels of these traits were associated with reductions in stress in the control group. One interpretation is that the reduction in stress over time simply reflects a drop in arousal. It is intuitively logical that a novelty seeking individual might habituate to the protocol more quickly and experience less arousal as the novelty wore off. The opposite pattern of findings within the same cluster of traits in the placebo versus control groups suggests another possible interpretation. This cluster of traits may be more malleable or responsive in general, but different contextual contingencies may activate different behaviours. Further research would be needed to test this interpretation.

6.1.9. Limitations and future directions

A key limitation of this study is the risk of cumulative Type 1 error. A number of personality measures were administered to a small sample, thus incurring a risk that findings are spurious. However, the cohesiveness of the constructs linked to responding across both self-reported and physiological measures of responsiveness, as well as the relative ease of interpretability, offers some confidence that findings are valid. Another limitation is that salience of the challenge as well as the placebo treatment could vary across people or personality types, and thus influence the relationships found. For example, for some may have experienced the mental arithmetic task as a non-noxious performance challenge, and thus suggestions regarding enhanced stress recovery would be less relevant. This issue is partly mitigated by the explicit verbal manipulation which suggested a reduced
That is, responses to the instructive suggestion can occur regardless of how noxious the stress challenge was.

Future research is needed to specifically test the interpretations offered from this study. The two faceted transactional conceptualisation of placebo responsiveness could be investigated by systematically manipulating contextual cues while recording levels responsiveness across the two facets. More research is needed to determine the best operationalization of the facets of responsiveness; and rather than organising findings into pain versus non pain paradigms, future work should aim to identify the salient contextual cues that differentially generate responses from different facets.

In conclusion, traits previously linked to placebo responding in pain paradigms were related to placebo responses in the current study, but in the opposite direction. A cluster of traits characterised by behavioural drive, extraversion, optimism and novelty or fun seeking appears to be germane to placebo responsiveness, but contextual stimuli may differentially activate responses from this ‘type’. Findings suggest that a rather than a ‘placebo personality’ it may be that responsiveness is better understood within a two faceted transactional model, in which different facets respond to different contextual contingencies. The development of a transactional model offers the possibility of predictive utility, thus progressing us towards the identification of stable predictors of placebo responsiveness.
6.2. Interim commentary: personality predictors of responding in non-pain contexts

The preceding paper demonstrated that in the context of recovery from psychosocial stress, it was individuals with lower levels of outwardly oriented traits and higher levels of the inwardly oriented traits that responded to the placebo manipulation. This pattern of responding stands in contrast to prior placebo analgesia research in which positive relationships between outwardly oriented traits and placebo responses have been found. Thus, results provide some initial support for the TMPR offered in Chapter 5, with an indication that rather than a single trait, placebo responsiveness may be better represented by two distinct, supraordinate facets, which respond to different environmental cues. Additionally, these findings extend the extant literature to describe personality predictors of placebo responses outside the pain context.

However, more research is still needed to obtain a better understanding of the patterns of responding to placebo manipulations in different contexts. To address this, another paper presenting personality predictors of placebo responses in the context of inflammatory skin reactions is presented next, with findings derived from Experiment II, as described in the introduction (Figure 1.1).

In selecting measures for this report, findings from the previous study were considered in conjunction with the TMPR and the more recent offerings from the placebo personality literature. Ego resiliency, a relative newcomer to the placebo personality literature [260], is described as indexing psychological resilience and adaptability [299] and is made up of items that include socialability, positivity, curiosity and openness, novelty seeking and less susceptibility to anxiety. Thus, ego resiliency not only resides within the outward orientation facet but it may be a good way to operationalise this facet. Ego resiliency was therefore added to the measures for the next study whereas empathy was excluded, given the context-specific relationships only demonstrated in placebo analgesic social observational paradigms. All other trait measures remained the same.
6.3. Personality predictors of responding in the context of inflammatory skin reactions


6.3.1. Abstract

**Objective.** This study investigated trait predictors of placebo responses in the context of inflammatory skin reactions. **Method.** This was a randomized, cross-over, experimental study using a deceptive placebo protocol. A healthy sample of volunteers (*N* = 48) completed online personality measures, then attended two laboratory sessions in which short-term inflammatory skin reactions were induced. One was a control session and the other the ‘treatment’ session in which a placebo cream was administered with the suggestion of a reduced skin reaction. A placebo response was defined as smaller skin reactions in the treatment as compared to the control session. Two traits were selected as possible predictors of placebo responses in consideration of the new two-faceted Transactional Model of Placebo Responding (TMPR) and in light of empirical and psychometric considerations. Neuroticism was selected to represent inward orientation, and ego resiliency to represent outward orientation, the two purported facets of responsiveness as offered by the TMPR. **Results.** Ego resiliency emerged as a consistent predictor of placebo responses in itch (*p* < .05) but neither trait predicted placebo responses in weal size. This is the first study to identify trait predictors of placebo responses in inflammatory skin reactions. Ego resiliency may typify greater placebo responsiveness; however, this may only be in certain contexts. Matching treatment approaches to bio-behavioural response tendencies may be useful clinically if the placebo component of traditional treatments can be enhanced.
6.3.2. Introduction

The experience of symptom improvement from the mere suggestion of therapeutic benefit, the placebo effect, offers the possibility of improving patient outcomes while reducing iatrogenic harm [300]. However, to maximise the clinical utility of this phenomenon, an important issue needs to be resolved. Not all persons respond to placebo treatments and the identification of stable, consistent, trait predictors of responding has been elusive [227].

Most research in this area has been conducted within placebo analgesia paradigms [152] and several distinct but conceptually cohesive predictors have been identified: optimism [255], extraversion [127], dopamine-related traits and genotypes [157, 246, 249], and ego resiliency [260]. Such findings suggest that rather than a unitary ‘placebo personality’, a cluster of traits may better represent placebo responsiveness [301]; however, it is not clear whether the same cluster of traits will predict responses outside the pain context. The ability to modulate pain responses varies across individuals ([156, 157], and the traits noted above may be specifically related to pain regulation rather than placebo responsiveness in general.

It is increasingly recognised that interactive models, in which environmental cues may interact with dispositional style to influence behaviour, may be needed to fully understand patterns of placebo responses [256, 266, 286]. A recently offered two-faceted Transactional Model of Placebo Responding (TMPR) [301] conceptualizes placebo responders as either inwardly or outwardly oriented, with behaviour motivated by either ‘avoid’ or ‘approach’ systems [273, 275]. In this view, both facets may derive benefit from placebo treatments, but may do so in the presence of distinct environmental cues.

Prior data appear to indicate that the outwardly oriented individual is more responsive to placebos [164]; however, as noted, most of this evidence is derived from pain-related paradigms. In other contexts, traits more characteristic of inward orientation, such as neuroticism, suggestibility, and absorption, have been related to greater placebo responding in psychosocial stress recovery [164], pulmonary function [135], and symptom improvement in multiple sclerosis patients [251]. There is some indication therefore, that placebo responsiveness may not be one-faceted, but more work is needed to investigate trait predictors of placebo responding in settings other than pain.

The aim of the current report was to investigate which traits predicted placebo responding in the context of local short-term inflammatory skin reactions. Participants completed personality measures before attending two laboratory sessions, a control and a ‘treatment’ (placebo) session. Skin reactions were induced in both sessions, but in the ‘treatment’ session, a placebo ‘antihistamine’
cream was applied with the suggestion that it would reduce the skin reaction. Personality traits were assessed as potential predictors of the placebo response, as operationalised by less itch and smaller weal size in the treatment versus control sessions.

6.3.3. Materials and Methods

**Design**

This was a randomized, cross-over, experimental study using a deceptive placebo protocol. Participants attended two 30-minute laboratory sessions (1-3 days apart), in which local type-1 hypersensitivity reactions were induced on the forearms with histamine. Participants were randomized to undergo either the control session first (Group 1), or the treatment session first (Group 2) in which the placebo manipulation was delivered. Note, a full description of the methods is published elsewhere [302].

**Participants, recruitment and enrolment**

After ethical approval, a healthy sample of 50 volunteers was recruited. The sample mean age was 22 years ($SD = 3.25$), predominantly female (79%), with Caucasians the largest ethnic group (42%), followed by non-Indian Asians (33%), Indian (15%), ‘Other’ (6%) and Māori and Polynesian (4%). Inclusion criteria were English-speaking adults aged between 18 and 45. Exclusion criteria were recent anti-histamine or anti-inflammatory medication, pregnancy, cardiac, autoimmune, psychological, or dermatological conditions, life-threatening allergies, injuries to either arm, or chronic illness.

**Procedure**

Before skin reactions were induced, information was provided to participants by video and a written information sheet. In the control session, participants were told the purpose of the session was to get an indication of their skin reactivity without treatment and that the cream applied to their arms was inert. In the treatment session, they were told that an anti-histamine treatment cream would be applied to their arms before the histamine was administered and that the cream would work to counteract the effects of the histamine, reducing itchiness and the size of the weal. In both sessions aqueous cream was applied to the anterior surface of the forearm and left to dry for two minutes before the histamine was administered to the same part of the arm. At 1, 3, 5 and 7 minutes after administration, self-
reported itch was measured. Photographs of the skin reaction were taken at 8 minutes. At the
completion of their second session, participants were provided with a $20 petrol voucher and thanked
for their time.

6.3.4. Measures

**Pre-experiment assessment of dispositional constructs**

The online questionnaire was completed approximately 1-2 weeks before the experimental session.
All scales and subscales were coded so that higher values indicated higher levels of the trait.

**BIS / BAS [273]:** measures individuals’ tendencies for behavioural inhibition (BIS) or behavioural
activation (BAS) systems. Participants rate agreement with 20 statements from: 1 (‘strongly agree’) to
4 (‘strongly disagree’). Reliability was adequate for all subscales (BIS $\alpha = .65$; BAS Fun $\alpha = .83$; BAS
Drive $\alpha = .89$; and BAS Reward $\alpha = .84$).

**Ego Resiliency Scale (Brief)[299]** assesses the trait of being psychologically resilient, such as being
able to manage and adapt to environmental demands and stressors. Items include aspects of
sociability, novelty seeking, emotional stability, and general positivity and openness to experience
(Cronbach’s $\alpha = .72$).

**EPQ-R Short Version [289]:** extraversion and neuroticism subscales. For each subscale participants
rated how much they agreed with 12 statements using a 1 (‘I agree a lot’) to 5 (‘I disagree a lot’) scale
(extraversion $\alpha = .89$, neuroticism $\alpha = .86$).

**Life Orientation Test Revised [290]:** assesses dispositional optimism via a 10-item scale with four filler
items. Participants rated each item on a 1 (‘agree a lot’) to 5 (‘disagree a lot’) scale ($\alpha = .80$).

**Modified Tellegen Absorption Scale [291]:** adapted from the original Tellegen Absorption Scale [292],
to a Likert scale [291]. Measures the extent to which an individual fully commits attentional resources.
Participants rate how frequently statements were true of their experience from 0 = ‘Never’ to 4 = ‘Very
Often’ (Cronbach’s $\alpha = .93$).
**Experimental measures**

*Weal size*

Photographs of the weals taken 8 minutes post-histamine administration were analysed using *Image J* (*National Institutes of Health, USA*), and horizontal and vertical diameters of each weal were measured using a calibration scale. An average of the three weals was taken as an estimate of weal area for use in analysis.

*Itch*

Participants’ self-reported itch was measured at 1, 3, 5 and 7 minutes post-histamine administration. Participants were asked to rate the itchiness using an 8-point scale from 0 = ‘not at all’, to 7 = ‘extremely’.

**6.3.5. Analytic approach**

To test for placebo effects, while controlling for the presence of allergies (given baseline differences between the groups, see [302]) and order effects (whether the order in which participants underwent control or treatment procedures affected outcomes), five 2 (Group) by 2 (Session) repeated measures ANCOVAs were conducted. The reported itch and weal data were coded so that each participant had scores for control (CX) as well as treatment (TX) sessions. The differences in weal size and itch were calculated with control session values subtracted from treatment session values to generate a difference score. Negative values indicated a reduction from control to treatment session (placebo response).

To test for trait predictors of placebo responding, 3-step forced-entry multiple regressions were conducted for each of the five outcome variables with the following steps: *(1) Group:* the order in which participants underwent control versus treatment sessions was entered in step one to control for order effects, *(2) Traits:* centred (z transformed) trait predictor variables were entered in step two (selection criteria described below); and *(3) Group by Trait* interaction terms were entered (Table 6.6).

**Selection of traits**

Nine trait variables were assessed but power considerations prevented the simultaneous inclusion of all in a regression analysis. Based on the two-faceted TMPR described in the introduction, two traits
were selected to best represent the hypothesized inward and outward facets of placebo responding. Given the degree of theoretical assumption involved in “choosing” predictors, an empirically-driven strategy involving three stages was employed:

(1) Correlations among all trait variables and placebo responses were assessed. Absorption, Drive, Ego Resiliency, Extraversion, Fun, Optimism and Neuroticism were all correlated with placebo responses (see Table 6.4).

(2) Then, given conceptual overlaps among the trait predictors and the possibility of regression model instability arising from multi-collinearity, correlations among the traits were assessed to determine which traits should be retained. Ego resiliency appeared to capture similar variance to that of extraversion, fun, and optimism (Table 6.5) and thus the latter three variables were removed, leaving Absorption, Drive, Ego, and Neuroticism.

(3) Finally, psychometric, empirical, and theoretical considerations were combined to select a single predictor for each of the inward and outward facets. **Ego Resiliency** was selected to represent the outward facet because it appears to capture the overlaps among related constructs (Table 6.5), and it is a good representation of the ‘outward’ facet as it indexes greater positive engagement with the external world and less susceptibility to anxiety. **Neuroticism** was selected to represent the inward facet because it is a good representation of an inwardly oriented, anxiety-sensitive individual and has better psychometric properties than the other anxiety-related measure (the BIS). Absorption was rejected as it is a complex multifaceted construct that may represent both inward and outwardly oriented facets [291].
Table 6.4.
Pearson’s product moment correlations between predictor and each outcome variable: the difference in itch from control to treatment sessions, at 1, 3, 5, and 7 minutes, and weal size, with control session values subtracted from treatment session values.

<table>
<thead>
<tr>
<th>Traits</th>
<th>Itch 1 minute</th>
<th>Itch 3 minutes</th>
<th>Itch 5 minutes</th>
<th>Itch 7 minutes</th>
<th>Weal size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grp1</td>
<td>Grp2</td>
<td>All</td>
<td>Grp1</td>
</tr>
<tr>
<td>Absorption</td>
<td></td>
<td></td>
<td></td>
<td>-.19</td>
<td>-.36+</td>
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<tr>
<td>BIS</td>
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<td></td>
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<td>.05</td>
<td>-.21</td>
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<tr>
<td>Drive</td>
<td></td>
<td></td>
<td></td>
<td>-.43**</td>
<td>-.49*</td>
</tr>
<tr>
<td>Ego</td>
<td></td>
<td></td>
<td></td>
<td>-.47**</td>
<td>-.54**</td>
</tr>
<tr>
<td>Extravert</td>
<td></td>
<td></td>
<td></td>
<td>-.37*</td>
<td>-.42*</td>
</tr>
<tr>
<td>Fun</td>
<td></td>
<td></td>
<td></td>
<td>-.34*</td>
<td>-.46*</td>
</tr>
<tr>
<td>Neuroticism</td>
<td></td>
<td></td>
<td></td>
<td>-.09</td>
<td>-.12</td>
</tr>
<tr>
<td>Optimism</td>
<td></td>
<td></td>
<td></td>
<td>-.14</td>
<td>-.08</td>
</tr>
<tr>
<td>Reward</td>
<td></td>
<td></td>
<td></td>
<td>-.28+</td>
<td>-.33</td>
</tr>
</tbody>
</table>

*p = .05 -.10
* p < .05
** p < .01
Table 6.5.

Pearson’s product moment correlations among trait variables.

<table>
<thead>
<tr>
<th></th>
<th>Absorption</th>
<th>BIS</th>
<th>Drive</th>
<th>Ego</th>
<th>Extravert</th>
<th>Fun</th>
<th>Neuroticism</th>
<th>Optimism</th>
<th>Reward</th>
</tr>
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<tbody>
<tr>
<td>Absorption</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIS</td>
<td>.092</td>
<td>.266</td>
<td>.236</td>
<td>.236</td>
<td>.117</td>
<td>.119</td>
<td>.185</td>
<td>-.073</td>
<td>.06</td>
</tr>
<tr>
<td>Drive</td>
<td>1</td>
<td>.042</td>
<td>-.28*</td>
<td>.185</td>
<td>.040</td>
<td>.41**</td>
<td>.040</td>
<td>-.099</td>
<td>.30*</td>
</tr>
<tr>
<td>Ego</td>
<td>1</td>
<td>.40**</td>
<td>.43**</td>
<td>.45**</td>
<td>.02</td>
<td>.30*</td>
<td>.30*</td>
<td>.46**</td>
<td></td>
</tr>
<tr>
<td>Extravert</td>
<td>1</td>
<td></td>
<td>.63***</td>
<td>.52***</td>
<td>-.39**</td>
<td>.44**</td>
<td>.42**</td>
<td>.30*</td>
<td></td>
</tr>
<tr>
<td>Fun</td>
<td>1</td>
<td></td>
<td></td>
<td>.47**</td>
<td>-.26</td>
<td>.44**</td>
<td>.42**</td>
<td>.30*</td>
<td></td>
</tr>
<tr>
<td>Neuroticism</td>
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<td></td>
<td></td>
<td></td>
<td>-.06</td>
<td>.21</td>
<td>.65***</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Optimism</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.31*</td>
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<tr>
<td>Reward</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < .05

**p < .01

***p < .001
6.3.6. Results

Results reported here are limited to the trait predictors of placebo responses (Table 6.6). A full description of preliminary analyses and results of tests for placebo effects is reported elsewhere [302]. Only the significant effects are described below. Note, results from Step 1 (Table 6.6), with only Group in the model, are not reported in detail below as no trait variables were entered in this step.

Itch at one minute

In Step 2 the model was significant ($p < .01$), with ego resiliency a significant individual predictor ($\beta = -.51, p < .001$). Higher levels of ego resiliency predicted a greater reduction in itch from control to treatment sessions. The model was not significant in Step 3 and there were no interaction (Group*Trait) terms ($p > .05$).

Itch at 3 minutes

In Steps 2 and 3 the overall model was not significant ($p > .05$); however, in Step 3, ego resiliency was a significant individual predictor ($\beta = -.41, p < .05$). Higher ego resiliency predicted a greater reduction in itch. No individual interaction terms were significant ($p > .05$).

Itch at five minutes

In Step 2 the model was not significant ($p > .05$); however, it was in Step 3 ($p < .01$). Both ego resiliency ($\beta = -.41, p = .03$) and neuroticism ($\beta = -.55, p = .01$) were significant individual predictors. Additionally, the interaction terms Group*Ego ($\beta = .61, p < .01$), and Group*Neuroticism ($\beta = .69, p < .01$) were significant. Those higher in neuroticism and ego resiliency had a greater reduction in itch; however, there were order effects. Inspection of the interaction indicated that both ego resilient and neurotic individuals had a reduction in itch when they underwent the control session first, but a slight increase in itch when they underwent the treatment session first.

Itch at seven minutes

In Step 3 the model was significant ($p < .01$). The interaction terms Group*Ego ($\beta = .52, p = .01$) and Group*Neuroticism ($\beta = .57, p = .01$) terms were predictive of greater reductions in itch. The regression slopes at minute seven followed the same pattern as at minute five.
Weal size

There were no trait predictors of weal size ($p > .05$).

Table 6.6.
Three step forced entry regressions for each outcome variable: the difference in itch from control to treatment sessions, 1, 3, 5, and 7 minutes, and weal size. Group entered as step 1, Traits entered in step 2, and a Group*Trait interaction term entered in step 3.

<table>
<thead>
<tr>
<th>Difference score</th>
<th>Step 1 (Group)</th>
<th>Step 2 (Trait)</th>
<th>Step 3 (Group*Trait Interaction term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itch 1 minute</td>
<td>$R = .50$, $R^2 = .25$, $F(1,46) = 15.15^{**}$</td>
<td>$R^2 \Delta = .27$, $F(2,44) = 12.02^{**}$</td>
<td>$R^2 \Delta = .007$, $F(2,42) = .29$</td>
</tr>
<tr>
<td>Itch 3 minute</td>
<td>$R = .25$, $R^2 = .06$, $F(1,46) = 2.98^{+}$</td>
<td>$R^2 \Delta = .03$, $F(2,44) = .73$</td>
<td>$R^2 \Delta = .07$, $F(2,42) = 1.82$</td>
</tr>
<tr>
<td>Itch 5 minute</td>
<td>$R = .17$, $R^2 = .03$, $F(1,46) = 1.30$</td>
<td>$R^2 \Delta = .008$, $F(2,44) = .18$</td>
<td>$R^2 \Delta = .25$, $F(2,42) = 7.52^{**}$</td>
</tr>
<tr>
<td>Itch 7 minutes</td>
<td>$R = .28$, $R^2 = .08$, $F(1,46) = 3.99^{+}$</td>
<td>$R^2 \Delta = .00$, $F(2,44) = .003$</td>
<td>$R^2 \Delta = .18$, $F(2,42) = 5.02^{*}$</td>
</tr>
<tr>
<td>Weal size</td>
<td>$R = .37$, $R^2 = .14$, $F(1,46) = 7.24^{*}$</td>
<td>$R^2 \Delta = .01$, $F(2,44) = .28$</td>
<td>$R^2 \Delta = .04$, $F(2,42) = 1.08$</td>
</tr>
</tbody>
</table>

$^{+}p < .05 - .10$

$^{*}p < .01$

6.3.7. Discussion

This study investigated trait predictors of placebo responses in the context of inflammatory skin reactions, using a transactional model of placebo responsiveness (the TMPR) to guide selection of predictor variables. With a framework suggesting there are two facets of responsiveness that may respond to different environmental cues, two traits were selected as potential predictors. Ego resiliency was chosen to represent outward orientation, and neuroticism for inward orientation.

Overall, ego resiliency emerged as a consistent predictor of placebo responses in itch. This finding is consistent with recent work in placebo analgesia that identified ego resiliency as a predictor of responses [260]. More broadly, ego resiliency clearly overlaps with the cluster of traits that have been linked to placebo analgesic responses [127, 157, 246, 249, 255], included within the ‘outward orientation facet of the TMPR [301]. Thus, results from the current study extend findings beyond pain into the realm of inflammatory skin reactions, and suggest that individuals characterised by social, positive, adaptable, and novelty seeking traits (outward orientation) may typify placebo responsiveness, at least in the context of itch and pain.

However, itch and pain processes may not be entirely distinct, as the opioid system plays a role in itch processing and may use the same neuromodulators and pathways [303]. Thus, histamine-
induced itch reactions could be considered to be within the domain of placebo analgesia, and outward orientation may only characterise placebo responsiveness in pain-related contexts.

The neuro-modulatory systems mediating responses may be one explanation for such context-specific responses. That is, dopaminergic systems have been suggested as a mechanism of placebo responses [28] and are known to be intertwined with pain systems [157]. The traits typified by outward orientation have a consistent theme of dopamine [157, 246, 249], and the ‘approach’ behavioural style is said to be mediated by dopamine systems [273, 277, 301]. Thus, it may be that outwardly oriented, dopamine-sensitive individuals are better able to activate or regulate pain-related regulatory networks in particular because of the underlying role of dopamine.

Alternatively, placebo responses may arise from an interaction between an individual and the nature of the cues in their environment. It has been established that contextual factors play a central role in the placebo phenomenon [22]. As posited by the transactional model [301] the presence of contextual cues that generate an internal versus external focus of attention may be one way in which placebo manipulations can differentially elicit responses from ‘inwardly’ versus ‘outwardly’ oriented individuals.

For example, a prior study used a noxious stimuli that was internally generated rather than externally applied (i.e., elevated heart rate from a psychosocial stressor), plus the suggestion that it would reduce heart rate. Being higher in neuroticism and lower in drive and optimism predicted greater responses [164] and thus it was more inwardly oriented individuals that responded to a manipulation focussing on internal states or sensations. In contrast, in the current study both the noxious stimulus and placebo treatment were externally applied. The local inflammatory skin reactions were generated on the surface of the skin, and a topical placebo cream was administered. The suggestion was that the skin reaction would be reduced in terms of a smaller weal size and less itch, both of which are perceptible on the external surface of the skin. The ego-resilient, outwardly-oriented individual may be differentially likely to respond to clear external cues of this kind. Relatedly, procedures employed in the current study share similarities with protocols employed in placebo analgesia studies. That is, with the administration of noxious stimuli on the arm and the suggestion of alleviation with a cream, the contextual cues offered to participants may be similar across the two paradigms. Thus, ego resilient (outwardly oriented) types may be responsive to these kind of cues. Future research would need to investigate this more directly.
While neuroticism also predicted less itch at five and seven minutes, there were order effects. Across both groups, persons high in neuroticism reported a reduction in itch from the first to the second session, regardless of the placebo manipulation. Such a finding may imply habituation to the protocol or, given the nature of neuroticism, a reduction in anxiety. These order effects were also present for those high in ego resiliency, which may also reflect a habituation response such as an increase in boredom. This habituation may have reduced physiological arousal, and could have resulted in reduced skin reactions by the five and seven minute measures.

In considering the clinical application of these results, there is thought to be a placebo aspect to all treatments, reflecting the non-specific effects of the therapeutic encounter and adding benefit over and above pharmacological ingredients and surgical or other interventions [21]. Consequently, one way in which the placebo phenomenon could be translated to clinical settings is by enhancing the placebo component of a treatment. Responsiveness and benefit could be enhanced by tailoring the way that the effects of treatment are framed such that they “match” the individual’s bio-behavioural style. For example, outwardly-oriented individuals may preferentially respond to cues such as the presence of novelty, or an externally-focussed suggestion regarding the effect of the treatment. In contrast, the more anxious, internally-oriented individual may do better without such novelty but, instead, benefit from clear suggestions regarding the effect of treatment on their internal state.

Limitations to this study include the crude measure of weal size and the use of a healthy student sample which may limit generalizability. The inclusion and measurement of more personality variables may have generated different results; however, the use of prior research and theory to generate the selection criteria enables greater confidence that the measures chosen are good candidates for placebo responsiveness.

In conclusion, this is the first study to identify trait predictors of placebo responses in inflammatory skin reactions. Ego resiliency predicted greater placebo responses, which is consistent with placebo analgesia research; however, the overlaps between itch and pain circuitry and the similarities between procedures employed across these two paradigms may mean responses in itch could be considered a ‘pain-related’ context. The nature of the environmental cues may differentially generate placebo responses from outwardly versus inwardly oriented individuals but further research is needed. Adjusting treatment approaches based on an individual’s bio-behavioural style represents a possible clinical application of the placebo phenomenon.
7. TESTING THE TRANSACTIONAL MODEL

The previous study found that ego resiliency predicted placebo responding in the context of experimentally-induced itch. This finding is consistent with results from a recent placebo analgesia study; however as noted, histamine-induced itch could be considered pain-related, due to the overlaps in the neural circuitry involved in itch and pain processes. Additionally, with a paradigm that administered noxious stimuli to the arm on two occasions then applied a cream to ameliorate the resulting symptoms, the procedures resemble those involved in experimental pain. That is, a common protocol in placebo analgesia paradigms is to repeatedly apply painful stimuli to the arm to ascertain individual baseline readings of subjective pain then apply a placebo cream with the suggestion it is an analgesic agent. Thus, the environmental cues offered in the itch study may be similar to those typically available in pain paradigms. While findings may indicate that outward orientation, perhaps typified by the construct of ego resiliency, is a better operationalisation of the placebo responsive type overall, this still may be only in certain contexts when particular cues are offered.

To recap to this point, the preceding chapters presented an overview and critique of the current placebo personality literature (Chapter 4) and the new, two-faceted Transactional Model of Placebo Responding (TMPR) (Chapter 5) as a possible means by which to incorporate personality theory into this research domain more systematically. As noted, this model suggests that more than one responder type may exist, and different personality types might respond to different cues in the environment. As such, the cluster of traits most often linked to placebo responding in prior work (outward orientation) might reflect the predominance of pain-related placebo research. To address this limitation, two studies were carried out in non-pain paradigms (Chapter 6), with findings indicating different personality characteristics may predict placebo responsiveness in contexts that appear differentially ‘relevant’ to different personality types. Such findings are consistent with the suggestion that there may be an interaction between dispositional style and environmental cues in responding to placebo treatments.

However, while measurement choices and aspects of the design of these two studies were informed by the TMPR, they were not direct tests of the model. Thus, the final study in the doctoral
programme presented in this thesis aimed to test the model directly by manipulating environmental (treatment) cues to specifically match the two different facets. In the study, participants were randomised to receive one of two placebo treatments, both containing the same substance (saline), but described as different treatment compounds. One treatment description was designed to match an outward orientation and the other to match an inward orientation.

Additionally, whereas both prior studies (Experiments I and II) were conducted in laboratory settings, the final study investigated placebo responding in a more naturalistic setting, with a take-home, self-administered placebo treatment. With a sample of individuals who were experiencing stress and anxiety arising from the demands of daily life, as well as a take-home placebo treatment, this context was notably different from those of experimentally-induced pain. Thus this study offered incremental value over the prior two studies in two ways: first, by offering a qualitatively different non-laboratory context and a protocol that approximated medical prescriptions; and second, by building on prior work and directly testing the hypothesis that different personality types might respond to different contextual cues.

Figure 7.1. A photo of the placebos used in Experiment III: ‘oxytocin’ and ‘serotonin’ treatment compounds delivered in an intranasal spray.
7.1. Testing the Transactional Model of Placebo Responding


7.1.1. Abstract

**Objective.** In harnessing the placebo effect for clinical benefit, more research is needed to determine who might be responsive to a placebo treatment. Recently, a two-faceted Transactional Model of Placebo Responding (TMPR) was offered, which suggests different personality types might respond to different contextual cues. The current study directly tested this model by manipulating treatment cues to match the two facets of responsiveness, inward and outward orientation. **Methods.** Physically healthy volunteers (*N* = 77) experiencing life stress were randomized to either the: (1) wait-list control, (2) ‘serotonin treatment’ group; or (3) ‘oxytocin treatment’ group. Both treatment groups received an ‘anti-stress’ intranasal spray (placebo). The ‘serotonin’ and ‘oxytocin’ treatments were designed to match the two facets (respectively), set out in the TMPR. The BIS/BAS scale was used as proxies for inward (BIS) and outward (BAS) orientation. It was hypothesised that high BAS types would be more responsive to the ‘oxytocin’ and high BIS types would be more responsive to the ‘serotonin’. **Results.** As expected, high BAS types had a greater response to the ‘oxytocin’ and low BAS types tended to have a greater response to the ‘serotonin’. Contrary to predictions, high BIS types also had a greater response to the ‘oxytocin’ treatment; however, elevated baseline anxiety in this group may have generated this interaction. **Conclusions.** Findings indicate interactions between personality type and environmental cues may contribute to placebo responding, but more research is needed to investigate possible operationalisations of responsiveness and the contextual cues to which different types may respond.
7.1.2 Introduction

There is now considerable evidence demonstrating that placebo treatments can exert meaningful effects on health outcomes [29, 121]. With primary care burdened by symptomatic individuals and psychologically-influenced conditions [2-5], placebos may become an essential part of future treatment repertoires. However, not everyone responds to placebo treatments [227] and one of the challenges preventing this phenomenon from being harnessed for clinical benefit is understanding which individuals might benefit from taking a placebo.

Recently, a new conceptualisation of placebo responsiveness was offered, the two-faceted Transactional Model of Placebo Responding (TMPR) [301]. This approach suggests responding to placebos arises from a transaction between an individual’s dispositional style and cues in their environment. In alignment with Gray’s bio-behavioural, stimulus-response model of personality [273, 275-277], the TMPR suggests there are two facets of responsiveness - inward orientation and outward orientation - that are governed by different neurological systems and which generate different responses to environmental stimuli. Inwardly oriented individuals are characterised by an ‘avoidant’ style, being sensitive to anxiety-relevant cues, and more oriented to their internal environment or experience. Conversely, outwardly oriented individuals are predisposed to an ‘approach’ style which generates a desire to interact with the external environment and move towards goals and possible rewards [301].

A review of the placebo personality literature [301] reveals more evidence for the outwardly oriented responder with traits such as ego resiliency [260], extraversion [127], fun, novelty-seeking, and behavioural drive [246], openness to experience [157], optimism [255], and a dopamine-related genotype [249] related to placebo responses; however, this work has almost exclusively been conducted within pain paradigms. Given the possibility of a transaction between dispositional style and environmental cues, pain paradigms may be offering particular cues to which outwardly oriented individuals are differentially responsive. For example, it may be that the offer of relief from painful stimulus represents a goal or reward that tends to elicit responses from the outwardly oriented individual.

Conversely, research in other settings has linked placebo responding to traits included within the inward orientation facet [301]. In multiple sclerosis patients, higher absorption was related to greater responsiveness [251]; in the context of pulmonary function in asthmatics, suggestibility was
linked to responding to the placebo suggestion [135]; a serotonin-related genotype was related to greater placebo responses in the context of social anxiety [247]; and in psychosocial stress recovery, behavioural drive and optimism were inversely linked to placebo responses [164]. Thus, there is some evidence to support the notion that placebo responsiveness is not best characterised by one personality type and that different cues in the environment may contribute to different patterns of responding for different types of person.

The possible importance of an interaction between disposition and environment in eliciting placebo responses has already been noted in placebo discourse [256, 266, 286]; however, studies directly investigating this possibility are scarce. One study found an interaction between personality and practitioner’s therapeutic style, with extraversion predicting placebo responses only in the augmented session in which the practitioner was empathic and caring [127]. Another research group have suggested an interactionist approach to placebo responding based on evidence that optimists respond to positively valenced cues [256] and pessimists respond to negative cues [287]. Beyond the valence of the expectancy manipulation and the practitioner style, the way in which a placebo treatment is described is also a contextual cue that could be manipulated to test for interactions between dispositional style and environmental cues in eliciting responses.

The current study aimed to test the TMPR by manipulating contextual cues in the form of treatment descriptors, to “match” the two possible facets of responsiveness described above. In the context of general psychological distress arising from the challenges of life (stress, anxiety and depressive symptoms), participants were randomized to receive one of two different placebo treatments: an ‘oxytocin’ compound designed to be aligned with an outwardly oriented disposition; or a ‘serotonin’ compound designed to correspond to inward orientation. The BIS/BAS scale [10], which assesses ‘avoid’ versus ‘approach’ behavioural styles [277], was used as a proxy for inward and outward orientations (respectively). It was hypothesised that those higher in BAS would have a greater placebo response to the ‘oxytocin’ placebo and those high in BIS would have a greater response to the ‘serotonin’ placebo.

7.1.3. Method

This was a randomized, controlled, non-laboratory study. All participants were randomized into one of three groups: (1) wait-list control group; (2) Treatment S (‘serotonin’); or (3) Treatment O (‘oxytocin’).
Those in the treatment groups were instructed to self-administer an intranasal treatment spray for three days in between pre- (Day 1) and post-treatment (Day 5) measures. Both sprays were placebos containing sterile saline (5%), but were described differently (see Procedures). The wait-list control group completed measures for five days without taking the treatment, but then commenced treatment once the wait-list protocol was completed. Randomization to group took place prior to the participant’s appointment. The research assistant (RA) who met with participants was not blind to group; however, all baseline and outcome measures were completed online after the session and away from the RA.

**Participants and Procedure**

The study was approved by the university’s review board and participants gave written consent after reading detailed information about what participation involved. All procedures contributing to this work comply with the Helsinki Declaration of 1975, as revised in 2008.

To recruit a sample of physically healthy individuals suffering from sub-clinical levels of psychological distress, advertisements were placed around a hospital research department and on a university intranet recruiting volunteers experiencing mild to moderate stress from life’s challenges. No course credit was offered for participation. Those suffering from chronic illness or who had a history of psychopathology were excluded. Of the 81 who initiated the treatment protocol, four dropped out (one from the control group, one from the ‘oxytocin’ group and two from ‘serotonin’). The final sample size was 77, with 33 participants in wait-list control, 22 in the ‘serotonin’ group, and 22 in the ‘oxytocin’ group.

After consent and enrolment, participants were scheduled to meet the RA for one 15-minute session. This session took place in clinical research rooms located within the university’s medical school. The RA gave a brief overview of the study, explaining that participants would receive an anti-stress treatment to reduce the symptoms and experience of stress and anxiety. After the RA checked exclusion criteria they informed participants which group they were in and provided an overview of the protocol. Whilst the two treatment groups were told to commence treatment on the following day, the wait-list control group were informed they would complete measures for five days and then commence their choice of the two treatments.

The two treatments were described to all participants as anti-stress compounds which stimulated their bodies to produce either serotonin or oxytocin, described as follows: (1) Treatment S
Serotonin is a neurochemical that is centrally involved in positive emotions. Serotonin helps regulate the stress response by suppressing negative stress hormones and generating positive moods; and (2) Treatment O (‘oxytocin’): Oxytocin is a hormone that is centrally involved in social bonding. Oxytocin helps regulate the stress response by promoting social engagement and generating feelings of trust and connectedness. As such, the two treatments were designed to appeal (respectively) to inwardly oriented individuals, by assisting with regulation of internal states; and to outwardly oriented individuals by promoting interactions with the external world.

All information was provided in a standardised verbal form by the RA, within a brief video, and in written form as part of ‘treatment packs’ which also included information about administration, storage, and dosage. Upon completion of the full protocol, all participants were provided with a $20 voucher to compensate them for their time, and were entered into a prize draw to win an iPAD-4. Participants were debriefed after all study data had been collected.

Summary of protocol
After their appointment (Day 1) participants were sent an email with a link to the first questionnaire, which assessed pre-treatment levels of perceived stress, anxiety, and symptoms of depression (see Measures). On Days 2, 3, and 4, the two treatment groups self-administered the spray as instructed and then on Day 5, all participants completed a final measure of stress, anxiety and depressive symptoms (post-treatment measures) via an email link. Once the 5-day protocol had been completed, the wait-list control group were informed that they could now commence taking the treatment spray.

7.1.4. Measures
Pre-experiment measures
Approximately one week before participants met with the RA they completed an online questionnaire that gathered demographic information, assessed health behaviours and several traits that have been linked to placebo responding in prior work: absorption [291]; ego resiliency [299]; extraversion, and neuroticism [289]; and optimism [290]. Ultimately only the BIS/BAS was selected to represent the possible facets of inward and outward orientation as explained in the analytic approach section below.
BIS / BAS [273]: is a psychometric proxy for Gray’s bio-behavioural approach/avoid model. It measures the individuals’ tendencies towards activation in behavioural inhibition (BIS) or behavioural activation (BAS) systems [275, 276]. Participants rate their agreement with 20 statements from: 1 (‘strongly agree’) to 4 (‘strongly disagree’). The BIS facet is measured by a 7-item subscale assessing sensitivity to anxiety relevant stimuli ($\alpha = .74$). The BAS facet ($\alpha = .84$) is measured by three subscales with four to five items in each: ‘Fun’ indexes novelty- and fun-seeking ($\alpha = .78$), ‘Drive’ indexes a ‘go getter’ approach ($\alpha = .77$), and ‘Reward’ assesses reward sensitivity ($\alpha = 84$). The BIS scale and the overall BAS scale, consisting of the three subscales combined, were used in analysis, with higher scores indicated higher levels of BIS and BAS.

**Outcome measures (mild to moderate psychological distress)**

**Stress:** The Perceived Stress Scale (PSS) [215] is a 10-item questionnaire designed to measure the extent to which participants perceive their lives to be stressful. Participants are asked to indicate on a 5-point scale how often (‘never’ to ‘very often’) they have thought or felt in certain ways in the last month. Higher scores indicate higher levels of recent perceived stress. Internal consistency for the PSS was good on Day 1 ($\alpha = .80$) and Day 5 ($\alpha = .86$).

**Depressive symptoms:** The Centre for Epidemiological Studies Depression Scale (CES-D)[216] assesses depressive symptoms in the general population. Participants rated how often they experienced symptoms of depression in the last week on a scale from 0 ‘rarely/none of the time’ (<1 day) to 3 ‘most/all of the time’ (5-7 days). Internal consistency for the CES-D was good was on Day 1 ($\alpha = .89$) and on Day 5 ($\alpha = .90$).

**Anxiety symptoms:** The Cognitive Somatic Anxiety Questionnaire (CSAQ)[217] assesses both somatic and cognitive symptoms of anxiety. Participants rate from 1 (not at all) to 5 (very much so) how much in the last week they have experienced somatic symptoms of anxiety (e.g., ‘I had diarrhoea’ and ‘my heart raced’) as well as anxiety related thoughts (e.g., ‘I worried too much over something that doesn’t really matter’). Internal consistency for the CSAQ was good on both Days 1 and 5 ($\alpha$s = .85).
7.1.5. Analytic approach

Preliminary tests for baseline between-group differences were conducted using one-way ANOVAs and chi-squared tests for independence (Table 7.1). Pairwise comparisons were corrected with LSD. To test for placebo effects (i.e., whether the treatment groups had a greater reduction in depressive symptoms, stress, and anxiety than controls), a one-way ANCOVA was carried out for each outcome variable, with post-treatment values (Day 5) the dependent variable, and the pre-treatment values (Day 1) controlled for. Main effects, means, and standard deviations for all variables are presented in Table 7.1. To test the hypothesis that inwardly versus outwardly oriented personality types would respond differently to the two different placebo treatments ('serotonin' and 'oxytocin'), 2 (Placebo Group) by 2 (Dichotomized Trait) ANCOVAs were conducted for each outcome variable and for both facets as described below.

Operationalisation of inward and outward orientation

The BIS and BAS scales were dichotomized using median splits. These high/low dichotomised variables were used as the independent variable in each of the ANCOVAs. To ensure that the BIS/BAS variables represented the best operationalisation of the inward and outward facets, the same approach was taken to test ego resiliency (outward orientation) and neuroticism (inward orientation) with analyses revealing a similar pattern of findings. Only the BIS/BAS was used in final analyses as it is more closely aligned with the TMPR.

Operationalisation of placebo responses

In order to detect a placebo effect, analyses needed to include the control group changes over the five day protocol. However, including control group participants in the ANCOVAs would have had the effect of demonstrating how different persons (e.g., those low or high in BIS or BAS) responded to stressors and challenges over time without treatment, which was not the aim of this study. Instead, control values were incorporated in the operationalisation by computing the treatment group’s change scores relative to the control group’s change scores. First, the control group’s mean change in each outcome variable was calculated by subtracting Day 1 from Day 5, such that a negative value would indicate a reduction in stress, anxiety, or depressive symptoms. Then, a relative change score for each treatment group participant was created by subtracting the mean of the control group’s change
from each of their change score (for each outcome variable), thus adjusting the treatment group’s change scores to represent change relative to the control group. These relative change scores for each outcome variable were used in analyses.

**Covariates**
Baseline tests revealed a difference in age between the control and the serotonin group ($p = .03$): however, age was not included as a covariate because there was no difference between the serotonin and oxytocin groups and a test revealed that including age did not affect the outcomes.

In order to quantify an individual’s dispositional tendency for either inward (BIS) or outward (BAS) relative to the other (as orthogonal systems), the counter trait for each predictor variable was added as a covariate to each ANCOVA. That is, when assessing BAS, the counter trait (BIS) was added as a covariate, and vice versa.

### 7.1.6. Results

**Sample Characteristics**
Participants were aged from 19 to 50 years of age ($M = 24, SD = 5.92$) and predominantly female (70%). NZ Europeans made up the largest ethnic group (53%) with Asian (including Indian, Sri Lankan, and Pakistani participants) the next largest group (40%) and the remainder describing themselves as ‘other’ (7%).

**Preliminary analyses**
Results from tests for baseline differences in outcomes, personality and demographics are reported in Table 7.I. Given the aim of investigating the interaction between trait (high/low BIS/BAS) and responses to the treatments (oxytocin/serotonin), t-tests were conducted to assess baseline between-group differences in the outcome variables with the data stratified by BIS and then BAS. Tests revealed a between-group difference in the anxiety measure for high BIS types ($t(20) = -3.77, p = .001, d = -1.60$). Those high in BIS randomised to the oxytocin group had significantly higher pre-treatment anxiety ($M = 47.40, SD = 9.23$) than the serotonin group ($M = 34.33, SD = 7.04$).
Table 7.1.
Tests for baseline differences between the groups in personality, demographic, health and outcomes; and placebo effects on outcome variables, with means, standard deviations, test statistics, and significance levels.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n = 33)</th>
<th>Serotonin (n = 22)</th>
<th>Oxytocin (n = 22)</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% female)</td>
<td>22/33 66%</td>
<td>16/22 73%</td>
<td>16/22 73%</td>
<td>.33</td>
<td>.85</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian vs non)</td>
<td>17/33 52%</td>
<td>12/22 55%</td>
<td>14/22 64%</td>
<td>.81</td>
<td>.67</td>
</tr>
<tr>
<td></td>
<td>Control M(SD)</td>
<td>Serotonin M(SD)</td>
<td>Oxytocin M(SD)</td>
<td>$F(df)$</td>
<td>$p$</td>
</tr>
<tr>
<td>Age</td>
<td>22.15(3.46)</td>
<td>25.68(7.27)</td>
<td>23.59(6.92)</td>
<td>F(2,74) = 2.44</td>
<td>.09</td>
</tr>
<tr>
<td>BMI</td>
<td>22.76(3.12)</td>
<td>22.64(3.09)</td>
<td>23.41(5.89)</td>
<td>F(2,74) = .24</td>
<td>.79</td>
</tr>
<tr>
<td>Perceived health</td>
<td>14.53(1.61)</td>
<td>13.77(1.74)</td>
<td>14.64(1.81)</td>
<td>F(2,73) = 1.75</td>
<td>.18</td>
</tr>
<tr>
<td>Dr visits (12 mths)</td>
<td>2.97(3.79)</td>
<td>3.50(5.26)</td>
<td>4.00(3.78)</td>
<td>F(2,74) = .39</td>
<td>.68</td>
</tr>
<tr>
<td>PSS (Day 1)</td>
<td>30.33(5.13)</td>
<td>29.23(5.82)</td>
<td>30.91(5.46)</td>
<td>F(2,74) = .55</td>
<td>.58</td>
</tr>
<tr>
<td>CES-D (Day 1)</td>
<td>18.27(9.10)</td>
<td>17.73(8.82)</td>
<td>19.59(10.27)</td>
<td>F(2,74) = .23</td>
<td>.79</td>
</tr>
<tr>
<td>CSAQ (Day 1)</td>
<td>33.33(9.24)</td>
<td>31.55(9.82)</td>
<td>35.77(13.01)</td>
<td>F(2,74) = .88</td>
<td>.42</td>
</tr>
<tr>
<td>Traits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIS</td>
<td>21.30 (2.99)</td>
<td>21.23 (3.19)</td>
<td>21.27 (3.83)</td>
<td>F(2,74) &lt; .01</td>
<td>.10</td>
</tr>
<tr>
<td>BAS</td>
<td>39.48 (4.76)</td>
<td>39.55 (5.97)</td>
<td>39.00 (5.68)</td>
<td>F(2,74) = .07</td>
<td>.93</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS (Day 5)</td>
<td>29.63 (5.95)</td>
<td>25.59 (6.86)</td>
<td>25.63 (5.85)</td>
<td>F(2,71) = 4.90</td>
<td>.01</td>
</tr>
<tr>
<td>CES-D (Day 5)</td>
<td>19.19 (9.30)</td>
<td>13.77 (9.91)</td>
<td>14.55 (9.79)</td>
<td>F(2,71) = 11.73</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>CSAQ (Day 5)</td>
<td>30.84 (8.41)</td>
<td>26.23 (8.37)</td>
<td>28.17 (9.35)</td>
<td>F(2,71) = 5.02</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

Tests for placebo effects

Results revealed main effects of Group for all three outcome variables (Figure 7.2). The placebo manipulation reduced depressive symptoms ($\eta_p^2 = .25$), anxiety ($\eta_p^2 = .12$), and perceived stress ($\eta_p^2 = .12$)(Table 7.1). Pairwise comparisons revealed that both treatment groups had greater reductions in depressive symptoms than controls ($ps < .001$). The oxytocin group had a significantly greater reduction in stress than controls ($p < .01$), with a trend for the serotonin group to have a greater reduction in stress than controls ($p = .07$). Only those in the oxytocin group had a greater reduction in anxiety than controls ($p < .01$) with a trend in this general direction for the serotonin group ($p = .11$). There was no difference between the two treatment groups in the outcome measures (Figure 7.2).
Figure 7.2. Change in symptoms of depression (CES-D), anxiety (CSAQ) and stress (PSS) by Group (Control, Serotonin, Oxytocin) with Day 1 (pre-treatment) subtracted from Day 5 (post-treatment) so that negative values indicate a reduction.

Testing hypotheses: trait by group interactions

It was hypothesised that across the three indices of psychological distress, high BAS types would have a greater response to the ‘oxytocin’ placebo than low BAS types; and high BIS types would have a greater response to placebo ‘serotonin’ than low BIS types.

Depressive symptoms

There was an interaction between BAS and Group \((F(1,38) = 11.35, p < .01, \eta^2_p = .23)\) with post-hoc t-tests revealing a difference between high and low BAS types in the oxytocin group. As hypothesised, high BAS types reported a greater reduction in depressive symptoms than low BAS types. In those taking ‘serotonin’ the difference between high and low BAS types was not significant \((p = .18)\); however, low BAS types tended to have a greater response than high BAS types who had almost no reduction in symptoms (Figure 7.3). Contrary to hypotheses there was no interaction between BIS and Group \((p = .10)\) (Figure 7.4).
Figure 7.3. Group (Serotonin and Oxytocin) by trait (low and high BAS) in change in depressive symptoms (Day 5 minus Day 1) relative to the control group’s change. Error bars are standard error of the mean.

Figure 7.4. Group (Serotonin and Oxytocin) by trait (low and high BIS) in change in depressive symptoms (Day 5 minus Day 1) relative to the control group’s change. Error bars are standard error of the mean.

Anxiety symptoms

There was an interaction between Group and BAS ($F(1, 38) = 5.76, p = .02, \eta^2_p = 13$). Post-hoc t-tests revealed a trend for a difference between high and low BAS types taking ‘oxytocin’. As hypothesised, those high in BAS tended to have a greater reduction in anxiety symptoms than those low in BAS.
There was no difference between high and low BAS types taking ‘serotonin’ ($t(20) = -1.11, p = .28$).

There was also an interaction between Group and BIS ($F(1, 38) = 10.86, p < .01, \eta^2_p = .22$). Post-hoc t-tests revealed a difference between high and low BIS in the oxytocin group. Contrary to hypotheses, high BIS types had a larger reduction in anxiety symptoms than low BIS types. In the ‘serotonin’ group, the difference between high and low BIS was not significant ($p = .13$); but high BIS types who received ‘serotonin’ tended to have the smallest reduction (Figure 7.6).

**Perceived stress**

There were no interactions between Group and either BAS ($p = .68$), nor BIS ($p = .63$).
7.1.7. Discussion

This study was designed to extend understanding of the personality factors associated with placebo responding. In particular, it tested the two-faceted Transactional Model of Placebo Responding (TMPR) by manipulating treatment descriptors to match the two hypothesized facets of responsiveness. Using the BIS/BAS scale to represent the inward and outward facets set out in the model, it was hypothesised that high BAS types would have greater placebo responses when taking an outwardly oriented treatment (‘oxytocin’), whereas high BIS types would be more responsive to an inwardly oriented treatment (‘serotonin’). Findings provide partial support for these hypotheses with some preliminary explanations offered below.

With regard to the effects on depressive symptoms, high BAS types had a greater response to ‘oxytocin’ compared with low BAS types, as hypothesised. Findings indicate that individuals with a greater outward orientation may be more responsive when a placebo treatment is positioned with an external focus and prompting engagement with one’s social world. Those less outwardly oriented did not respond as well to this description, with a trend for a greater reduction when taking the ‘serotonin’, a treatment described as helping to regulate internal states. These findings provide some support for an interactive model of placebo responsiveness in which dispositional style might interact with contextual cues in generating responses to a placebo treatment.

Figure 7.6. Group (Serotonin and Oxytocin) by trait (low and high BIS) in change in anxiety symptoms (Day 5 minus Day 1) relative to the control group’s change. Error bars are standard error of the mean.
Contrary to hypotheses however, high BIS types also appeared to be more responsive to 'oxytocin', at least in reducing symptoms of anxiety. Higher baseline anxiety in this group may help explain this finding, with elevated anxiety creating an opportunity for greater reductions across the five day protocol. The reason for this initial anxiety is not known, but one can speculate that for high BIS (anxious) types, being 'prescribed' a compound that was described as prompting social interactions may have increased their initial (pre-treatment) anxiety. This interpretation is consistent with the anecdotal observations of some participants who reported that they were ‘relieved’ when they found out they were randomised to the serotonin group.

Regardless of this interaction, those high in BIS had virtually no response, in terms of anxiety reduction, to the ‘serotonin’, which is contrary to hypotheses. One explanation is that for those high in BIS, the serotonin treatment manipulation may have had the effect of turning their attention inward because of its focus on internal states and symptoms. Anxiety-prone individuals already have a tendency to focus on internal bodily sensations and report greater symptomology [304, 305], and research has shown that increasing somatic focus can generate higher symptom reporting [306]. Thus for high BIS individuals, taking ‘serotonin’ may have differentially generated an elevated internal focus which resulted in their noticing and reporting greater symptomology.

Findings across the three outcome measures suggests the intended match between the serotonin placebo and the inwardly oriented ‘BIS’ type was not successful. In explanation, it may be that the serotonin manipulation was not suited to the core nature of BIS. For example, considering Gray’s approach/avoid bio-behavioural model from which the BIS/BAS was derived, rather than cues that focussed on internal states, cues that were more specifically designed to appeal to the harm or punishment avoidant aspect of the BIS type [234] may have been more successful in generating behavioural responses. Alternatively it may be that the BIS is not comprehensive enough to adequately represent inward orientation. The BIS indexes anxiety whereas the inward orientation construct includes other aspects such as an internal focus and possibly being more suggestible. This indicates that the construct validity of the BIS (as a proxy for inward orientation) may be weaker than desirable.

Finally, there were no interactions between BIS or BAS and the two treatment groups in reductions in stress. One possible explanation for this finding is that psychological stress originates from the perception that life’s demands exceeds ones resources [307] and may thus reflect a
differential contribution from environmental factors. That is, stress is more ‘external’ than depressive or anxiety symptoms, and changes in stress may reflect changes in the presence of stressors rather than changes in internal states such as the experience of symptoms. This may have made it harder to detect interactions between such changes and personality traits.

Overall, findings indicate that while personality variables could influence placebo responses, the TMPR may not capture all the subtleties of responsiveness. That said, issues with operationalisation may be obscuring findings and, as a model in its infancy, more research that is specifically geared towards testing the model with a priori predictions is needed. Once operationalisation issues are addressed and the cues that elicit responses from the two facets are identified, the TMPR has the potential to offer clinical utility. By positioning treatments to match patient’s bio-behavioural styles, the placebo component of any treatment could be enhanced [21], thus maximising the overall therapeutic benefit.

Limitations to this study include the use of a predominantly student sample, which limits generalisability to the wider population. It must also be acknowledged that the measurement of additional personality variables and the selection of different traits for analyses may have yielded different results. The development of the two treatment descriptions to align with inward and outward orientation were conceptually appropriate but relatively artificial and removed from a real clinical setting. Future research might manipulate other, more ecologically valid treatment cues, such as manipulating the degree of social interaction between the patient and practitioner. Future work should also continue to seek more optimal operationalisations of two the facets of responsiveness.

In conclusion, this study offers a direct, a priori test of how dispositional traits may interact with contextual cues to generate placebo responses, as well as the first empirical test of the TMPR. Findings suggest that there are interactions between personality type and treatment cues in the generation of placebo responses but further research is needed.

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8. DISCUSSION

This research programme investigated: (1) the capabilities of placebo suggestion outside the context of pain; and (2) the personality characteristics that predict placebo responses in these other contexts. One systematic literature review and three experimental studies were conducted (Figure 1.1), with results detailed within seven reports presented in this thesis. Here, in this final Discussion chapter, findings and commentary will be integrated and discussed in terms of empirical and theoretical contributions as well as the limitations of the research and possible future research directions that could be pursued. Then, to address the overarching context in which this doctoral research was conducted, the clinical and health applications of the findings will be considered before a final concluding section.

8.1. Empirical contributions

Findings from this research programme extend the extant placebo literature by offering several incremental contributions. Further, these results may add to current thinking about suggestion-induced placebo effects by highlighting the possible importance both of explicit instructions and of having an experience-based understanding of the suggestive instruction, as discussed in the following sections.

8.1.1. Incremental offerings

Experiment I demonstrated the placebo effect in the context of physiological recovery from a psychosocial stressor (Chapter 3.1). With increases in vagal activity after the suggestion of enhanced recovery, the results contribute to a smaller body of work demonstrating suggestion-induced effects on autonomic function [213].

Experiment II revealed that a suggestive placebo protocol can reduce the experience of histamine-induced itch (Chapter 3.3). Prior research had demonstrated a placebo-induced reduction in itch through the use of suggestion and conditioning procedures [189], but not suggestion alone. With histamine-induced inflammatory skin reactions serving as a proxy for allergic immune processes, this
finding contributes to a very small body of work demonstrating suggestive placebo effects on immune parameters [45].

The findings from Experiment III suggest that placebos can be effective outside the laboratory for the alleviation of stress, anxiety, and depressive symptoms (Chapter 3.5). There have been few placebo studies employing either the method (a take-home placebo treatment) or the outcome measures (naturalistic stress, anxiety, and depressive symptoms) used in this study. The use of a stand-alone placebo protocol to alleviate depressive symptoms adds further evidence to data from clinical trials indicating that placebo treatments can be useful in mental-health conditions. The use of a protocol that more closely approximates medical treatment regimes in which patients are required to take a treatment home and self-administer it within their normal routine further increases the ecological ‘reach’ of these findings.

In addressing the second research question, the findings from this research programme suggest that different personality types may be more likely to respond to different placebo manipulations. For example, in recovery from acute psychosocial stress, lower optimism and less behavioural drive predicted greater reported benefits from the placebo treatment; whereas in the reduction of itch, it was greater ego resiliency that predicted greater placebo responses. Variability in the predictors of placebo responding is a pattern seen in prior placebo personality research in which multiple, distinct traits have been linked to placebo responses. A critical review of this literature (Chapter 4.2) prompted the development of a new conceptualisation of placebo responsiveness (Chapter 5.1) which provides a framework for understanding how traits might interact with environmental cues to generate placebo responses. This model represents the key theoretical contribution of this research programme and will be discussed in detail in Chapter 8.2.

8.1.2. The importance of explicit suggestive instruction

Findings across the three studies demonstrated the ability of placebo suggestion to impact indices of autonomic function, itch, and psychological distress. Taken together, one interpretation that can be offered is the possible importance of using explicit suggestive instruction in placebo protocols. That is, providing detailed instructions and an explanation of how a treatment works may be part of how a pharmacologically inert treatment can generate psychobiological changes.
All three studies employed this approach. In the first study for example, participants were provided with information about the physiological stress response, how heart rate variability was a measure of this response, and how the nasal spray contained serotonin which plays a key role in enhancing recovery from stressors. This information was given during the experimental procedures and was repeated in the information sheet participants received prior to enrolment in the study.

Similarly in Experiment II, explicit information regarding the effects of the placebo antihistamine cream was provided. This information detailed how the cream worked to block signals from the skin and suppress the inflammatory response in terms of both itch and weal size. In the final study, participants were given information about stress responses and were told they would receive a compound that stimulated the production of either serotonin or oxytocin as substances that would help to regulate the experience of stress and anxiety.

Thus, the inclusion of detailed information about how a treatment is expected to work may be an important part of suggestion-induced placebo effects on some parameters. The delivery of a placebo treatment without explicit and meaningful instructions may explain why some placebo protocols fail to generate effects, as observed in the context of itch [195] and autonomic function [153, 213]. Providing participants with this kind of detail may increase its salience so that sufficient attention is paid to the treatment instructions, or it may increase expectations of benefit, which can increase the odds of experiencing clinical benefit from a placebo [47, 308]. This type of explicit suggestive instruction may also facilitate the activation of appropriate self-regulatory processes, such as the top-down networks thought to mediate some expectancy-induced placebo effects [40, 115] as described in the introduction (Chapter 2.4).

However, while explicit instruction may be an important contributor of suggestion-induced placebo effects, it may also be that in order to modulate certain parameters, especially those which are not so common in an individual's everyday life, a concrete, experience-based understanding of the suggestion instruction is needed, as discussed next.

8.1.3. The importance of an experience-based understanding of suggestive instruction

In interpreting findings across Experiments I and II, in which attempts were made to modulate physiological processes after the experimental induction of noxious stimuli, some insight may be
offered by considering the possible importance of having an experience-based understanding of the suggestive instruction.

For example, in Experiment I participants underwent a baseline stress task in the control session, which took place prior to the ‘treatment’ (placebo) session. Thus, when the placebo manipulation was delivered, participants knew specifically what the suggestive instruction meant in the context of the noxious stimuli they were experiencing. They had already experienced the stress test and had an experience-based understanding of what the suggestive instruction referred to. This concrete knowledge may have enabled activation of the appropriate self-regulatory systems, such as an increase in vagal activity to enhance recovery from the stressor.

In Experiment II, local skin reactions were induced in two separate sessions, one control and one ‘treatment’ (placebo) session. In the treatment session, participants received the suggestive instruction that the antihistamine cream applied to the arm would reduce the size of the weal and the experience of itch. Participants underwent the two sessions in randomised order, with half the sample undergoing control procedures before the treatment session and the other half in the reverse order. Order effects were observed such that only the group that underwent the control procedures first had less itch at the first measurement point (one minute), and a reduced weal size. In explanation, only this group had an experiential understanding of the nature of the noxious stimuli when they received the suggestive instruction in the second session. For the other group, with no prior exposure to the particular procedures involved in the study, the suggestive instructions regarding reduced weal size and itch may have been too abstract to be meaningful.

Whether this is framed as a learning process, related to the facilitation of response expectancies, or as the activation of self-regulatory networks (Chapter 2.4), it may be that an experienced-based understanding of what the suggestive instruction refers to is needed to generate changes in certain parameters. Building on previous research and discourse which highlighted the role of prior treatment experience in contributing to placebo effects [61], this interpretation suggests that in some cases, prior experience or exposure with the stimuli in the placebo manipulation may also be necessary. Future work could test such interpretations by systematically manipulating participants’ prior exposure with novel placebo procedures.

Overall then, the empirical contributions from this research programme described above tend to imply the need for explicit instructions and/or an experience-based understanding of the suggested
effects in order to influence certain outcomes, which may offer some insight into the generation of suggestion-induced placebo effects.

8.2. Key theoretical contribution

8.2.1. The Transactional Model of Placebo Responding (TMPR)

The TMPR was developed after a review of the placebo personality literature uncovered a lack of theoretically-driven research and the possible need for a new conceptualisation of placebo responsiveness. The TMPR suggests that rather than a unitary trait, placebo responsiveness may be better conceptualised in terms of two facets - inward orientation and outward orientation - which are differentially responsive to different environmental cues. Inwardly oriented individuals are characterised by being avoidant, anxiety-prone, sensitive to punishment, more oriented to their internal environment, and with behaviour that may be mediated by serotonergic systems. Conversely, outwardly oriented individuals are predisposed to having an ‘approach’ behavioural style which generates movement towards goals and possible rewards, a desire to interact with their external environment, and behaviour that may be mediated by dopaminergic systems (Chapter 5.1). The TMPR aims to address conceptually the possibility of an inherent interaction between disposition and environment in responding to placebos.

While the TMPR informed aspects of the design of the first two experimental studies, it evolved over the course of the research programme and was not directly tested until the final study. In this study, participants were randomised to receive one of two treatment compounds, the descriptions of which were designed to match the two purported facets of placebo responsiveness. Partial support for the model was demonstrated; however, other results were contrary to hypotheses. As was noted earlier, this may have been due to a poor ‘match’ between the placebo manipulation and the BIS/BAS scales which were selected as proxies for inward/outward orientation. One possibility is that the contextual cues offered within the manipulation were not suitable (addressed below in Chapter 8.2.3); however, issues around how to best operationalise the inward and outward facets of the TMPR may also have contributed to results, as discussed next.
8.2.2 Operationalisation of inward and outward orientation

In the final study, inward and outward orientation were operationalised using the BIS/BAS measure, a psychometric proxy for Gray's bio-behavioural avoid/approach model [273, 275, 276] (Chapter 5). This measure was a natural choice given the conceptual and structural alignment between Gray's model and the TMPR. Consistent with hypotheses, those high in BAS had a greater response to the outwardly positioned placebo treatment ('oxytocin') than low BAS types, suggesting that those high in behavioural activation may differentially respond to treatment manipulations that focus on engagement with one's external social world.

However, contrary to hypotheses, high BIS types did not respond to the inwardly positioned 'serotonin' but instead also had a greater response to the 'oxytocin' placebo. In explaining this finding, the elevated baseline anxiety in this group may have provided an opportunity for a much greater drop over the treatment protocol; however, it may also imply the need for refinement of the operationalisation of inward and outward orientation via the BIS/BAS. Although caution is certainly warranted, this may be a psychometric issue rather than a conceptual problem for the TMPR as it is consistent with the general challenges associated with the psychometric measurement of bio-behavioural systems. Beyond the placebo literature, the question of how to psychometrically index Gray's bio-behavioural system is an issue that has been raised but not yet properly resolved [309].

Psychometric measures can be 'blunt' and unsuited to measuring the complexities of human bio-behavioural systems [38].

One approach which has received recent attention is to identify placebo responders through the use of genotyping. While offering less practical utility than simple self-report measures, this approach may be more closely aligned with a bio-behavioural model of behaviour. Both dopamine-related [157, 249] and serotonin-related [247, 248, 310] genotypes have been associated with placebo responsiveness in different contexts. In attempting to align this approach with psychometric indices, several overlapping traits have been identified which appear to adequately index the dopaminergic (outwardly oriented) type, insofar as they predict placebo responses in pain-related contexts [38]. However, the serotonergic type has received less attention. While a good self-report measure of anxiety-related serotonergic genotypes may exist [311] this has yet to be tested in the context of placebo responsiveness. Thus, while there is evidence to support the notion that responsiveness is
two-faceted, and characterising these facets as inward (serotonergic) or outward (dopaminergic) types [38, 225] may be useful, more research is needed.

Alternately, it may be that the BIS subscale is not comprehensive enough to adequately capture the construct of inward orientation. For example, while the BAS has 13 items and measures three facets of novelty seeking, reward sensitivity and behavioural drive, the BIS has only seven items and is essentially an anxiety construct. Conceptually, the inward orientation facet includes other aspects such as an internal focus and possibly aspects of acquiescence and suggestibility (see Chapter 5.1). Thus, some sort of composite measure that embraces a broader range of items, including avoidant tendencies, an internal focus, and suggestibility, may be a better way to capture the inward orientation facet.

Finally, it is possible that responsiveness is better conceptualised as a continuum from inward to outward orientation (or low to high levels of behavioural activation), with behaviour governed to a lesser or greater extent by dopaminergic approach systems. While the BIS/BAS, avoid/approach model suggests the presence of two orthogonal facets, this may not best represent the nature of placebo responsiveness. Findings from Experiment I found lower levels of behavioural drive and lower optimism to predict responses in the context of psychosocial stress recovery. In the final study, those high in BAS responded to the outwardly oriented placebo treatment (‘oxytocin’), and those low in BAS had a reduction in symptoms with the ‘serotonin’ treatment. More research is needed, but in considering the best operationalisation of responsiveness, the possibility of a continuum should also be considered.

Identifying the best psychometric indices of placebo responsiveness in general, as well as for the inward and outward facets of the TMPR, are complex challenges that require further research; however, in the meantime, how different contextual cues may be contributing to differential patterns of responding will be discussed.

8.2.3. The nature of environmental cues eliciting responses

The TMPR broadly suggests that the different contextual cues implicit in placebo manipulations may be a key reason for varied patterns of responding across different individuals; however, the particular cues to which personality types might be responsive are not yet clear. In consideration of this issue, a
return to Gray's bio-behavioural model of personality may offer some clarity in interpreting findings across the works.

As was noted earlier, Gray's [275, 276] temperament theory describes two neurological systems, behavioural inhibition (BIS) and behavioural activation (BAS), that generate underlying predispositions to respond to environmental cues [273], as typified by ‘approach’ or ‘avoid’ behaviour. The approach (BAS) system is thought to generate movement towards goals and be responsible for the experience of positive feelings when cues for impending reward are presented [273, 277]. The avoid (BIS) system is thought to control the experience of anxiety in response to anxiety-relevant cues, and be sensitive to signs of punishment and novelty [273, 276].

Thus, the presentation of a treatment as offering either the possibility of attaining a reward versus the possibility of punishment or the avoidance of an aversive stimulus may be a key factor in differentially eliciting responses from the two facets. Consistent with this interpretation: a study that employed a reward/punishment paradigm found anxious types were more sensitive to losing cues than winning cues and put in less effort in the reward condition [312].

In the current research programme, in Experiment I, the negative evaluative aspect of the stressor and the delivery of authoritative instruction about effects by the researcher may have been more salient for the inwardly oriented, avoidant type, who are likely more ‘motivated’ to avoid punishment and thus had a greater response to treatments presented in this manner. Conversely, the suggestion of enhanced recovery (reduced heart rate) from the stress task as the possible ‘reward’ may not have been sufficiently appealing to the outwardly oriented approach types.

In Experiment II, the relief from itch offered in the placebo manipulation provided a goal (reward) for the outwardly oriented to respond to; whereas for the inwardly oriented individual, who is less motivated by possible rewards and more by avoiding punishment, these cues may not have been as relevant. Additionally, in this study, instructions and information about treatment effects were not delivered by the research assistant but by video and written information. Thus, while the outwardly oriented still had an approach goal (itch reduction) to respond to, the inwardly oriented did not have the opportunity to ‘comply’ with authoritative instruction and avoid ‘punishment’.

In the final study, the treatment descriptors were more deliberately positioned so that they ‘matched’ the inward and the outward orientation facets; however, with the hypotheses only partially supported, findings indicate that this matching process was not entirely successful. The cues offered
within the manipulation may have needed to be more explicitly geared towards the bio-behavioural personality style in the true ‘avoid’ and ‘approach’ sense as suggested above. Future research is needed to test the use of specific reward/punishment or approach/avoid goals in attempting to elicit differential responding from the inwardly versus the outwardly oriented types.

8.2.4. The possibility of different mediating networks in inward and outward responders

In addition to the suggestion that inwardly and outwardly oriented individuals may respond to the presence of different environmental stimuli, there is the possibility that placebo responses in these two facets may be mediated by different neuro-modulatory systems. Prior work has implicated dopaminergic systems as being specifically relevant to the ‘approach’ or outwardly oriented type, whereas serotonergic systems are implicated in the functioning of the ‘avoid’ or inwardly oriented type [273, 277]. Thus, it is worth speculating that the two facets may employ two different neuro-modulatory networks in generating placebo responses.

Most of the traits included in the outwardly oriented facet are related to dopamine [20-23, 47, 48] and behavioural responses in this type may well be mediated by dopamine systems [50]. Dopamine has been clearly implicated as a pathway in some placebo responses [28, 38] and may mediate effects via the tonic activation of dopamine neurons [313] or dopaminergic reward pathways [114]. Taken together, it may be that for the outwardly oriented individual, the activation of dopaminergic systems in the presence of potential rewards is a general mediatory pathway that leads to the alleviation of noxious symptoms and the generation of placebo responses. The overlaps between dopamine and opioid systems [49] and the role of reward circuits in initiating opioid networks [23] may be part of the reason why prior work has implied that the dopaminergic type is responsive in pain-related contexts.

Conversely, for the inwardly oriented type the alleviation of noxious stimuli may occur via a serotonergic regulatory system. Serotonergic systems are a significant contributor to individual differences in regulating emotion and behaviour, especially negative emotionality [312]. It may be that the inhibition of negative emotions might have a systemic tonic effect. The experience of stress and anxiety can generate a range of noxious physiological symptoms through activation of the hypothalamic-pituitary-adrenal pathway [108] and influence the immune system, which may have negative impacts on health [45]. Thus, when given a placebo treatment with the suggestion of
symptom amelioration, it may be that the inhibition of stress and anxiety networks reduces noxious symptomology and may even assist with healing processes [45].

Thus, while the outcome is similar (symptom alleviation), different mediating systems may be involved in generating placebo effects in outwardly oriented as compared to inwardly oriented types. Because of this, the two types may be ‘better’ at responding in different contexts; or even possibly limited to responding in contexts utilising dopaminergic or serotonergic systems, as appropriate [38].

In summary, in addition to contributing to thinking about the types of persons who respond to different types of placebo contexts and offering a framework for organising what are often quite fragmented findings, the current thesis may also contain implications for understanding placebo mechanisms. As these are speculative interpretations, future research is needed to investigate these notions as well as those raised earlier in this thesis. Further research is also needed to address the limitations to this research programme, as discussed next.

8.3. Limitations and future directions

Although the work presented in this thesis makes several contributions to placebo research, the studies are not without their limitations. In this section, the general (methodological) limitations will first be considered along with suggestions for further and improved research. To follow, the TMPR will be discussed in terms of future research directions that might advance understanding of who might be responsive to a placebo and in the presence of what contextual cues.

8.3.1. Methodological limitations

First, across the three experimental studies, the findings are limited in their generalisability and clinical applicability by the use of physically healthy, mostly student samples. For example, the relative youth of the participants means that the results may not be generalisable to older individuals. Age does not appear to be a significant factor in placebo effects [314], but in attempting to translate findings to a broader community sample, age homogeneity must be acknowledged as a potential limitation. Relatedly, as university students, participants represent a certain socio-economic group which may not generalise to the wider population. For one, the knowledge and intelligence level of this group is likely to be higher than the general population, and this might affect the impact of particular
instructions. For example, the central use of neurotransmitters within the suggestive placebo
manipulation is likely to be much more meaningful and engaging for students (particularly in a sample
comprised of predominantly psychology and medical students) than for members of the general public.

More broadly, findings from studies using healthy samples cannot be easily translated to
patient populations. As noted in the individual discussion and summary sections of each paper in
Chapter 3, further research is needed to test whether the findings offered in this thesis translate to
patient samples. Further, the results offered by this programme need to be replicated in order to
achieve proper scientific validity.

Another limitation to this research programme is the use of fairly small sample sizes in each
study; however, there are time, resource, and logistical drawbacks associated with research
conducted within a doctoral programme. Further, the exploratory nature of this research necessitated
several smaller studies rather than one large one. In addition to the demonstration of statistically
significant effects which can be affected by power, the selection of personality traits was affected by
this consideration. With a large sample (or with greater financial incentives to encourage participation
and completion) it would be possible to measure a larger number of personality variables, and with the
inclusion of previously unmeasured traits different findings may have resulted.

With regard to the search for a ‘placebo personality’, it must be acknowledged that while this
thesis investigated whether stable individual differences (i.e., traits) might be predictive of placebo
responding, studies in this research programme were not designed to directly address the question of
consistency in placebo responsiveness [227]. To properly test the notion that placebo responsiveness
is a consistent dispositional trait, the same group of individuals would need to be put through a
number of placebo manipulations. It also should also be acknowledged that findings from this research
programme do not necessarily translate to the question of which personality types are responsive to
placebo conditioning paradigms.

8.3.2. Testing the TMPR: future research directions

The TMPR was developed after a systematic literature review of the placebo personality indicated the
possible need for a new conceptualisation of placebo responsiveness. As a model in its infancy, more
research is needed to test the overall scientific utility of the TMPR. More specifically, research is
needed to both determine the optimum operationalisations of the facets of inward and outward orientation as well as to identify the most salient contextual cues to which each facet may respond.

The TMPR was developed relatively early in the doctoral programme and over time, as data was gathered and thinking progressed, the model evolved such that focus on the overarching ‘permeability’ construct offered (see Chapter 5.1) was replaced by attention to the two facets of inward and outward orientation. The term permeable was used to describe a perviousness to factors such as practitioner suggestions and treatment rituals, with permeable individuals thought to be responsive to placebos in the presence of appropriate environmental cues, whereas the ‘impermeable’ individual may not be responsive to placebo treatments at all. Future research might aim to pick up this thread, for example by investigating whether there is a personality type which is consistently unresponsive to placebo treatments. If such a type exists, this information could be useful clinically in identifying those who would benefit from a purely pharmacological treatment approach [315], as well as providing important information for people conducting drug efficacy trials. The efficacy of a specific pharmacological agent could be more easily ascertained with placebo responses controlled for with the use of impermeable (placebo non-responsive) participants.

With the aim of operationalising the two facets of responsiveness, future research might recruit an appropriately large sample so that individual items that best characterise both the inward and the outward responders can be identified through statistical tests. For example, it might be a grouping of individual items from a range of different measures that offers the best composite measure for inward as well as outward orientations. The challenges associated with employing self-report indices of a bio-behavioural response system were noted earlier and remain an on-going issue for future research. The use of genotyping to characterise responsiveness may yield useful results and be fruitful in a research setting, if not entirely practical in a primary care setting.

A further area that requires future research attention is the identification of the environmental cues to which individuals are likely to respond. The practitioner style, noted to be a centrally important factor in some placebo effects [121, 127], was not the focus of this research programme, but remains an important contextual cue that could be experimentally manipulated. Prior work has shown that in the context of relief from IBS symptoms, being extraverted predicted responses but only in an extended, augmented session in which the practitioner was empathic [127]. While a lack of empathy is unlikely to be a useful treatment approach, the inwardly oriented responder may benefit from a more
authoritative and directive treatment approach rather than an interactive, socially oriented therapeutic session. Future research could manipulate levels of social interaction within a placebo protocol to assess whether social interactions of different kinds elicit differential responding from different types. As noted earlier, the positioning of a treatment or the use of approach/reward versus avoid cues could also be manipulated experimentally to examine whether these types of cues elicit differential responding.

In summary, future research might aim to replicate results in a community sample, a wider range of patients or conditions, and use larger samples to ensure that all existing effects are detectable. Future research might also aim to investigate some of the mechanistic pathways offered earlier, including the importance of explicit instruction and having an experience-based understanding of the suggestive instruction. With regard to the TMPR, future research could aim to explore the best operationalisations of inward and outward orientation, as well as systematically manipulate contextual cues while recording levels of responsiveness to ascertain the most salient contextual cues that elicit responses from different types. Findings from such studies could facilitate the translation of placebo effects to clinical settings and maximise the clinical utility of placebos, as discussed next.

8.4. Clinical applications

The question of how to translate the placebo effect for clinical benefit continues to be an ethical and practical challenge [100, 193]. While more research is needed, findings from this research programme offer some ways the placebo effect could be utilised for clinical value.

First, findings suggest that intranasal placebo sprays can be useful for the management of mild to moderate psychological stress and stress-related ailments. Psychological stress is involved in many primary care complaints and work-related stress is now a major public-health problem [2]. Further, the link between stress and immune function has been established [316], with chronic activation of the stress response possibly leading to health problems [109, 181, 317]. As such, the question of how to treat psychological stress is important in both physical and mental health contexts. The alleviation of short-term, moderate psychosocial stress via a pharmacologically inert nasal spray could be leveraged in a therapeutic setting to aid individuals suffering from sub-clinical levels of stress and anxiety.
Given that placebos can alleviate noxious symptoms, they could also be useful in the management of conditions that are symptomatic and heavily influenced by psychosomatic factors. For example, the finding that a placebo cream can reduce the experience of itch may be useful as an adjunctive tool in the management of chronic idiopathic skin conditions. As was noted in the introduction, psychosocial factors contribute to the experience and exacerbation of itch and dermatological conditions [6, 191, 192]. Placebo creams could be utilised in this context either alongside medicinal ointments (e.g., steroid creams) to provide intermittent relief, or in a titration process so that dosages (i.e., the pharmacological component of an ointment) can be reduced or gradually eliminated [38, 318]. While a placebo cream may not be able to resolve underlying allergic processes, if it can alleviate the experience of itch then it could provide short-term relief and help reduce scratching behaviours, which can exacerbate such conditions. More indirectly, given the role of stress and anxiety in skin conditions such as urticaria, the use of placebo treatments to help with alleviation of stress and anxiety may positively influence such skin conditions.

Findings from Experiment III study suggest that placebos may be useful in the context of treating moderate anxiety and depression, which also plague primary care. As adjunctive tools, placebos could be used during drug washout phases, or as an extra device that patients could self-administer for acutely stressful events. The demonstration that a stand-alone placebo treatment can reduce symptoms of depression in a healthy sample helps bridge the gap between the considerable evidence for placebo responses in anti-depressant trials and the use of placebos in the clinical treatment of depression. However, despite these promising findings, the ethical problems associated with deception [97, 100, 319] must first be overcome before placebos can be employed in patient samples.

One way to overcome the ethical issues with placebo treatments is to use open placebo designs in which an explanation is provided to patients regarding the nature of the treatment they are taking. While this may negatively influence efficacy [137], such designs have been shown to be capable of producing benefit. For example, IBS patients experienced clinical improvements from a treatment they were told was inert but had been shown by rigorous scientific testing to be clinically beneficial [126]. A recent study demonstrated that benefits arising from a conditioned placebo response could be retained even after participants were told the agent contained no analgesic
properties 304]. More research is needed to investigate the efficacy of open placebo treatments in a larger range of conditions and populations.

Building on the notion that there is a placebo component to any treatment [21, 236], another way that the placebo effect might be utilised for clinical benefit is by capitalising on the factors that generate improvements in the absence of pharmacologically active agents [148]. If the placebo component of a treatment could be enhanced, the overall therapeutic benefit of standard-care treatments may also be enhanced. Findings from the current research suggest that one way that the placebo component of a treatment could be maximised is by using suggestive instruction that is both meaningful and explicit. For example as described earlier, in all three experimental studies participants were given detailed stories or meaningful narratives about the treatments and how they worked. The importance of meaning in generating placebo effects has been noted, with individuals thought to be responding to the meaning behind a placebo treatment, rather than the treatment itself [59]. Thus, instead of telling an individual that they will take X to have an effect on Y, a meaningful story with some sort of explanation of how it works may be part of how a pharmacologically inert treatment can generate benefit.

However, in attempting to position a treatment for maximum benefit, the possibility that different personality types will respond to different contextual cues, which is the central tenet of the TMPR, should be considered. For example, outwardly-oriented individuals may preferentially respond to cues such as: the presence of novelty; a focus on the rewarding properties of the treatment; a goal to ‘approach’; or an externally-focussed suggestion regarding the effect of the treatment. In contrast, the more anxious, internally-oriented individual may benefit from clear authoritative suggestion with benefits positioned in terms of loss prevention, or in such a way that participants can avoid ‘punishment’. As described earlier, more research is needed to determine the specific cues to which participants and patients might respond, as well as the best way to identify the inwardly and outwardly oriented responder in a clinical setting.

With the need for more research noted, findings suggest that it should be possible to harness the placebo effect for therapeutic benefit. Whether as an adjunctive tool to or a stand-alone treatment that can be administered without deception, placebo treatments could be a useful tool for symptomatic and mental-health related ailments; for conditions that incur risks of iatrogenic harm; and for those that inflict substantial burden on the modern healthcare system.
Against the backdrop of a healthcare system burdened by symptomatic and mental-health related conditions, the placebo effect represents a possible health tool that could be used to increase therapeutic benefit. However, the bulk of research into the placebo effect has been conducted in the context of experimental pain, and while this paradigm has yielded important information, the findings are not necessarily generalisable to other conditions and ailments. In order for the placebo effect to be harnessed more broadly for therapeutic benefit, a greater understanding is needed of the power of the placebo in other health settings, as well as who might be responsive to placebo treatments in these contexts. Within this research programme, one systematic review and three experimental studies were conducted to investigate these two questions.

Overall, both research questions were answered, with results offering both empirical and theoretical contributions to the extant placebo literature. First, with the demonstration of suggestion-induced placebo effects in the context of physiological recovery from acute psychosocial stress, itch, and stress, anxiety and depressive symptoms in a naturalistic settings, the first research question was addressed. Second, a new conceptualisation of placebo responsiveness was offered with the Transactional Model of Placebo Responding, which suggests that there are two facets of responsiveness (inward and outward orientation) that interact with environmental cues to generate different patterns of responding.

More research is needed in order to replicate the findings demonstrated in this research programme; to overcome limitations associated with the use of healthy, young, student samples; and to continue to work towards translating placebo effects to clinical settings with approaches such as open placebo designs and patient samples. More research is also needed to test the TMPR and determine the best operationalisation of inward and outward orientation as well as to identify the most salient contextual cues to which these individuals might respond, thus maximising an individual’s response to a therapeutic encounter.

One aim of medical treatments is to improve a patient’s experience by alleviating the symptoms or distress associated with illness, and while placebos may not be able to cure diseases, they do appear to able to achieve these goals [47]. The question of whether placebo treatments can offer clinical utility or therapeutic validity has been raised [48-50] and the answer, I think, is yes.
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<tr>
<th>#</th>
<th>Authors &amp; year</th>
<th>Sample size and sex</th>
<th>Age M (SD)</th>
<th>Design (randomization, and controls)</th>
<th>Description of placebo manipulation and treatment</th>
<th>Outcome</th>
<th>Personality variables</th>
<th>Rationale for personality measure</th>
<th>Main personality related finding</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Colloca &amp; Benedetti, 2009</td>
<td>48 (100% F) Non-patient</td>
<td>22.6 (4.7)</td>
<td>Randomised: 3 placebo treatment groups: (1) suggestion, (2) observation: (3) conditioning.</td>
<td>Suggestion, observational, and conditioning. Placebo analgesia, light cues to indicate pain/analgesia.</td>
<td>Self-report pain rating (HR measured but not manipulated)</td>
<td>Empathy</td>
<td>Not mentioned.</td>
<td>Placebo response in social observational condition associated with empathic concern. Relationship did not exist in suggestion and conditioning groups. No other relationships with empathy.</td>
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<td>3</td>
<td>Geers et al, 2007</td>
<td>56 (68% F) Non-patient</td>
<td>~20</td>
<td>Randomised 3 groups: (1) treatment + expectancy (2) treatment + no expectancy (3) no treatment control.</td>
<td>Suggestion. Placebo sleep therapy.</td>
<td>Self-report symptoms (sleep quality)</td>
<td>Optimism, Social Desirability</td>
<td>Prior research which suggests that higher optimism should be associated with greater responding to a positive expectation (e.g., placebo manipulation).</td>
<td>Optimism positively related to post placebo symptom scores in the placebo expectation group. Optimism not related to pre placebo symptom score (change scores not analysed). Social desirability unrelated.</td>
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<td>4</td>
<td>Geers et al, 2010</td>
<td>116 (52% F) Non-patient</td>
<td>20 (3.4)</td>
<td>Quasi randomised: optimists (M+1SD) and pessimists (M-1SD) randomised 2 groups: (1) deceptive expectancy and (2) no expectancy.</td>
<td>Suggestion, Placebo analgesic cream.</td>
<td>Self-report pain rating HR/BP measured but not manipulated</td>
<td>Optimism</td>
<td>Prior research and optimism association with active behavioural and mental coping.</td>
<td>Optimism associated with lower pain ratings after deceptive manipulation in expectancy group and not in control condition. No effect on HR/BP.</td>
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<tr>
<td>5</td>
<td>Hyland et al, 2008</td>
<td>251 (80% F) Non-patient</td>
<td>37 (11.9)</td>
<td>Randomised 3 groups: (1) spiritual treatment (2) neutral treatment (3) affirmative treatment.</td>
<td>Suggestion, Placebo therapy (flower essence therapy) for wellbeing.</td>
<td>Self-reported improvemen t (‘feeling better’)</td>
<td>Spirituality Optimism</td>
<td>Prior research, and spirituality as motivationally concordant with alternative therapy.</td>
<td>No main effect of spirituality, but evidence for motivational concordance hypotheses. Optimism not related to outcomes.</td>
</tr>
<tr>
<td>6</td>
<td>Kelley et al, 2009</td>
<td>297 (75% F) IBS patients</td>
<td>38 (14)</td>
<td>Randomised 3 groups: (1) limited placebo acupuncture, (2) augmented placebo acupuncture, (3) wait-list control.</td>
<td>Suggestion Placebo acupuncture (relief from IBS symptoms).</td>
<td>Self-report IBS outcomes</td>
<td>Extraversion, Neuroticism, Openness to Experience, Agreeableness Conscientiousness</td>
<td>Five Factor Personality Inventory measured as an index of ‘patient characteristics’.</td>
<td>Extraversion, agreeableness, openness to experience, and female gender associated with placebo response, in the augmented group. Regression analysis revealed extraversion sole significant predictor (in augmented group).</td>
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<td>7</td>
<td>Leigh et al, 2003</td>
<td>80 (17 included) (65% F) Asthma patients</td>
<td>46.85 (14.3)</td>
<td>Quasi randomised: High and low suggestives. Cross-over 3 sessions: (1) sham bronchodilator, (2) sham bronchoconstrictor and (3) real bronchoconstrictor.</td>
<td>Suggestion. Placebo bronchoconstrictor and bronchodilator.</td>
<td>Self-report Borg dyspnea scale and Forced expir volume.</td>
<td>Primary Suggestibility</td>
<td>Prior work documenting the role of suggestion in asthmatics (and allergy).</td>
<td>Reduction in FEV after placebo bronchoconstriction for 5/8 suggestive and 1/9 suggestion resistant. No group difference after placebo bronchodilation or in breathlessness after placebo bronchoconstriction.</td>
</tr>
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<td>8</td>
<td>McCann et al, 1992</td>
<td>30 (100% M) Non-patient</td>
<td>22 (1)</td>
<td>Cross-over 3 treatment sessions (1) anxiolytic, (2) simple placebo (3) placebo with extra suggestion. No base stress test or no-treatment control.</td>
<td>Suggestion. Placebo anxiolytic pill.</td>
<td>HR and systolic BP Cattells 16 Factors of Personality, Somatization</td>
<td>Prior research.</td>
<td>Placebo responders classified as &lt; 10% change in SBP/HR pre to post stressor). No difference between placebo and treatment response. Difference in submissiveness-dominance continuum (responders more submissive). Lack of a no treatment control means can’t be attributed to placebo response.</td>
<td>Placebo responders classified as &lt; 10% change in SBP/HR pre to post stressor). No difference between placebo and treatment response. Difference in submissiveness-dominance continuum (responders more submissive). Lack of a no treatment control means can’t be attributed to placebo response.</td>
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<td>9</td>
<td>McNair et al, 1979</td>
<td>241</td>
<td>26.4</td>
<td>Quasi-controlled (control group data taken from wait list). Cross-over: (1) anxiolytic / anti-depressants and (2) placebo pill.</td>
<td>Implicit expectation (pill taking). Placebo pill.</td>
<td>Distress (anxiety, depression, tension) and mood</td>
<td>Acquiescence</td>
<td>Prior research.</td>
<td>Acquiescence related to change in mood and distress in placebo group but not in control group. High acquiescent individuals obtained greater relief from placebo treatment than those low in acquiescence.</td>
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<td>10</td>
<td>Morton et al, 2009</td>
<td>62 (57% F)</td>
<td>25 (3.5)</td>
<td>Randomised 2 groups: placebo and control. 2 sessions with 3 phases in each: pre, conditioning and post.</td>
<td>Suggestion and conditioning. Placebo analgesic cream.</td>
<td>Self-reported pain rating.</td>
<td>Optimism Neuroticism Introversion Extraversion Social Desirability</td>
<td>Prior research and link between optimism and expecting positive outcomes.</td>
<td>Optimism correlated with placebo response in second session only. State anxiety, optimism and extraversion were significant predictors of placebo response (reduction in pain ratings) in second session. Social desirability not related.</td>
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<td>12</td>
<td>Owens et al, 2011</td>
<td>110 (78% F)</td>
<td>46 (21-64)</td>
<td>Cross-over (randomised order). 2 sessions: (1) treatment and (2) placebo treatment. NB: pooled results from multi-site trial.</td>
<td>Suggestion (implicit expectancy). Sham electromagnetic pulse device for relief from MS symptoms.</td>
<td>MS Quality of life outcomes / symptoms (fatigue, pain and spasticity).</td>
<td>Absorption Negative Affect</td>
<td>Absorption scorers have enhanced self-regulation capacities that might be engaged towards a therapeutic outcome.</td>
<td>Placebo responders (upper quintile on MS symptom improvements) higher in absorption than non-responders and had more confidence that the placebo was the active device. Negative affect differences marginally significant (responders higher).</td>
</tr>
<tr>
<td>13</td>
<td>Schweinhardt et al, 2009</td>
<td>22 (100% M)</td>
<td>22.2 (4)</td>
<td>Cross-over. 3 sessions: conditioning, testing, and measures. 2 phases in the testing session: (1) expectancy and (2) no expectancy (control)</td>
<td>Suggestion and conditioning. Placebo analgesic cream.</td>
<td>Self-reported pain rating and neural activity (MRI).</td>
<td>Dopamine-related trait (fun, drive, novelty seeking, reward responsiveness and harm avoidance)</td>
<td>The role of dopamine in placebo analgesic responses.</td>
<td>Placebo analgesic response correlated with the ‘dopamine-related’ trait. Gray matter density correlated with the magnitude of placebo analgesia as well as the ‘dopamine-related’ trait.</td>
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<td>15</td>
<td>Whalley et al, 2008</td>
<td>71 (67% F) Non-patient</td>
<td>20.6 (5.4)</td>
<td>Cross-over (randomised order). 2 sessions, 2 trials in each session (placebo and no treatment control).</td>
<td>Suggestion. Placebo cream for painful pressure.</td>
<td>Self-report pain ratings.</td>
<td>Acquiescence Absorption</td>
<td>Prior research and face validity of absorption and acquiescence as indexes of placebo responsiveness.</td>
<td>Placebo effects significantly associated with response expectancy but not with acquiescence or absorption. Absorption was related to expected pain relief at time one.</td>
</tr>
<tr>
<td>16</td>
<td>Hunter et al, 2013</td>
<td>60 (100% F) Non-patient</td>
<td>27 (7)</td>
<td>Randomised, 4 groups: (1) social observation on video recording, (2) social observation in person, (3) verbal suggestion, and (4) control.</td>
<td>Learning and suggestion. Placebo electrode for painful shocks.</td>
<td>Self-report pain ratings.</td>
<td>Empathy</td>
<td>Prior placebo research.</td>
<td>Placebo analgesic scores were strongly correlated with empathic concern only in the live observation group.</td>
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<td>17</td>
<td>Pecina et al, 2013</td>
<td>47 (60% F) Non-patient</td>
<td>26 (5)</td>
<td>Randomised in order and counterbalanced: 2 pain conditions and 2 placebo conditions each</td>
<td>Expectancy (but participants blind to condition). Placebo injection for painful isotonic saline.</td>
<td>Self-report pain, cortisol plasma, PET scans.</td>
<td>Anxiety (trait) BIS/BAS Ego resiliency Neuroticism Extraversion Openness Agreeableness Conscientiousness Optimism</td>
<td>Prior placebo research, links between dopamine neural structures and placebo analgesic responses, and link between personality traits and behavioural risk/resiliency and treatment responses</td>
<td>Aggregate of scores from Ego-Resiliency, NEO Altruism, NEO Straightforwardness (positive predictors) and NEO Angry Hostility (negative predictor) scales accounted for 25% of the variance in placebo analgesic responses. Relationships between higher levels of these traits and greater placebo-induced activation of m-opioid neurotransmission found from brain imaging.</td>
</tr>
<tr>
<td>18</td>
<td>Yu et al, 2014</td>
<td>48 (60% F) Non-patient</td>
<td>26.4 (3.6)</td>
<td>All subjects had control session and then conditioning and test sessions</td>
<td>Associative learning. High/low cues and painful heat.</td>
<td>Self-reported pain and fMRI.</td>
<td>Neuroticism, Extraversion, Openness, Agreeableness Conscientiousness COMT polymorphism</td>
<td>Prior research and links between neural systems involved in dopaminergic, opioidergic and placebo analgesic processes.</td>
<td>COMT genotype, and openness scores predicted changes in pain ratings.</td>
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