Relaxation and Wound Healing

A Randomised Controlled Trial Evaluating the Effectiveness of Virtual Humans in Delivering Relaxation to Improve Skin Barrier Recovery and Reduce Stress

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Abstract

Virtual humans are a form of artificial agent that is starting to be used to deliver e-health interventions. Several early studies show promising feasibility, but research designs have been preliminary to date. Therefore, more randomised controlled trials (RCTs) are needed to evaluate their effectiveness in delivering psychological interventions and improving health outcomes.

The aim of this study was to evaluate the effectiveness of a brief relaxation intervention delivered by a virtual human recording compared with a real human audiotape and a control group on wound healing and stress in a healthy community sample.

An RCT with a mixed factorial design was conducted. One hundred and fifty-nine healthy adults aged between 18 and 60 years (*M* =26.04*)* participated in a 90-minute session, during which they completed questionnaires and underwent a non-invasive tape-stripping procedure to disrupt the skin barrier, followed by a 20-minute recovery period. Participants were randomised to (1) relaxation delivered by a Digital Human, (2) relaxation delivered by human audiotape (3) reading magazines during the recovery period. A series of psychological questionnaires collected self-reported stress, relaxation, anxiety and pain, satisfaction, engagement, and open-ended responses; a wrist sensor wrist measured heart rate (HR) and electrodermal activity (EDA) and saliva samples collected stress hormones salivary cortisol (sCort) and alpha-amylase (sAA).

Results indicated no significant differences in skin barrier recovery (SBR), psychological or physiological stress measures between the delivery methods. However, the Digital Human and audiotape groups had significantly greater relaxation following the relaxation session, superior to the control group. Anxiety was significantly more reduced, and satisfaction and engagement levels were greater in the audiotape group. Additional open-ended responses indicated that the appearance and mismatch in lip-syncing of the Digital Human made some people feel uneasy and could be improved.

The findings demonstrate a virtual human's ability to relax people, comparative to traditional audiotapes in an RCT. The study provides suggestions to improve virtual humans' delivery of relaxation interventions and provides future experimental design recommendations. Ultimately, these findings encourage future studies to explore further the effects of an

interactive virtual human to deliver relaxation and improve health outcomes, particularly in highly stressed or clinical wound samples.

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List of Abbreviations

ACTH – Adrenocorticotropic Hormone

ANS – Autonomic Nervous System

CRF – Corticotropin-Releasing Factor

CSBM – Cognitive Stress Management

EDA – Electrodermal Activity

GI – Guided Imagery

HPA – Hypothalamic-Pituitary-Adrenal

HR – Heart Rate

NE – Norepinephrine

PMR – Progressive Muscle Relaxation

PNS – Parasympathetic Nervous System

PTSD – Post Traumatic Stress Disorder

RCT – Randomised Controlled Trial

sAA – Salivary Alpha-Amylase

SAM – Sympathetic-Adreno-Medullar

SBR – Skin Barrier Recovery

sCort – Salivary Cortisol

SD – Standard Deviation

SNS – Sympathetic Nervous System

VAS – Visual Analogue Scale

Chapter I: Virtual Humans

Thesis Overview

Virtual humans are highly realistic animated computer agents capable of conducting verbal conversations with people and show early feasibility and acceptability for delivering business and health interventions. RCTs are needed to evaluate the effectiveness of virtual humans at delivering psychological interventions compared with other delivery options. This thesis aimed to investigate the effects of a relaxation exercise delivered by a virtual human on wound healing and stress-related outcomes compared to the same relaxation exercise delivered by a human recorded audiotape and control condition (reading magazines). Wound healing offers a clinically relevant health outcome that is impaired by psychological stress and can be improved through relaxation techniques.

The introduction to this thesis describes prior research on virtual humans, stress, wound healing, and relaxation interventions and presents the current study's rationale. Chapter I defines eHealth and mHealth and introduces chatbots and virtual humans as artificial agents to deliver health interventions. The later section of this chapter focuses on virtual humans - their benefits, design considerations, and current healthcare applications. The second chapter describes the wound healing process, the stress response, and how stress is theorised to influence wound healing. The third chapter then discusses stress reduction interventions, focusing on relaxation, and outlines the evidence for the effects of relaxation on health outcomes before reviewing relaxation in the context of wound healing. The final chapter presents the study's rationale, aims, and hypotheses.

eHealth and mHealth

Due to the increasing strain on the healthcare system from overpopulation, ageing, increases in long-term health conditions, lack of resources and the current COVID-19 pandemic, not all patients can access adequate, affordable, or timely healthcare (Bradbury et al., 2014; Fagherazzi et al., 2020; Luxton, 2020). With increases in the number of people living with long-term health and mental health conditions, overpopulation and ageing, the demand on the healthcare system is increasing exponentially. Healthcare providers may not be able to provide timely or sufficient support to patients as demands overwhelm an already understaffed and underfunded healthcare system. Considering the exacerbation of illness and stress during the COVID-19 pandemic, alternative ways to provide healthcare are greatly needed. Technology offers a delivery platform that can augment existing healthcare by providing accessible and affordable care and support to a greater number of patients. As patients are already beginning to use the internet and mobile apps to access healthcare, continued research is needed to evaluate the efficacy and acceptability of these platforms as they develop.

e-health (electronic health) is a term that describes the use of technology and electronic means as communicative and informative tools to assist healthcare delivery (Eng, 2001; Mitchell, 2000; Oh et al., 2005). While the definitions of eHealth vary across the literature, e-health is commonly used as an umbrella term to encompass the range of delivery platforms, namely the internet (Karyotaki et al., 2021; Lustria et al.,2013; McCall et al., 2021), telemedicine (Thase et al., 2020), mobile apps (Lau et al., 2020; Weisel et al., 2019), VR (Rizzo & Shilling, 2017), robots (Broadbent et al., 2009; Robinson et al., 2015), or artificial agents (Bendig et al., 2019; Sagar et al., 2014). For eHealth platforms to be effective, they need to fit alongside other health communication, be easy to use, and be appropriate for diverse patient and ethnic populations (Kreps & Neuhauser, 2010).

m-health (mobile health) is a subgroup of eHealth that refers to mobile devices (e.g., mobile phones, patient monitoring devices or wireless devices) to support healthcare and public health practices. Often these devices are used to deliver health information, monitor health conditions (e.g., medication or symptoms), communicate with patients, or collect service data (Kay et al., 2011; Mirza & Norris, 2007). Given that 95% of the world's population has access to a mobile network (ITU, 2021), using mHealth platforms can be a convenient and accessible way to deliver health interventions. However, the diversity and the sheer number of applications have resulted in an oversaturated market with very few backed with robust evidence (Lau et al., 2020). Lack of randomisation, adequate sample sizes, theoretical rationale and efficacy measures are methodological issues that make it difficult to assess their effectiveness in improving health outcomes. In addition, mobile interventions often have low engagement after first use and outside clinical trial contexts, preventing them from becoming "sticky" and undermining their potential benefits (Lau et al., 2020; Milne-Ives et al., 2020).

Artificial Agents

Recent technological advancements have seen the development of more interactive, naturalistic, and humanistic platforms called artificial agents. Artificial agents with social interfaces may offer advantages for ongoing engagement in remote interventions compared with simple mobile apps. This section will explore chatbots and virtual humans as two types of artificial agents.

Chatbots

A chatbot (or conversational agent) is an automated interactive interface designed to communicate with patients through text or speech-based dialogue (Morgan, 2017). Powered by machine learning and natural language processing, chatbots can engage in structured conversation with patients based on patient speech or text input (Laranjo et al., 2018). Chatbots are typically used on smartphone messaging applications or websites (Car et al., 2020), making them a convenient, low cost, and low maintenance platform that can mimic human conversational dialogue (de Cock et al., 2020; Ly et al., 2017; Maher et al., 2020).

Pilot trials demonstrate that chatbots are feasible and acceptable methods of supporting disease self-management and wellbeing (Griffin et al., 2020), delivering positive psychology to young adults undergoing cancer treatment (Greer et al., 2019), delivering CBT to adults with panic disorder and delivering lifestyle modification interventions (Klos et al., 2021; Maher et al., 2020). More robust trials have shown effectiveness in reducing distress, stress (Gaffney et al., 2014), depression (Fitzpatrick 2017; Gaffney et al., 2014), anxiety (Fitzpatrick 2017; Gaffney et al., 2014; Greer et al., 2019), opioid use and pain intensity (Anthony et al., 2020). One study observed that psychological well-being and perceived stress only improved when participants adhered to the chatbot intervention, highlighting that technology uptake and engagement may be essential in its effectiveness (Ly et al., 2017). Measuring how patients accept and engage with eHealth platforms can help understand their likely real-world uptake. While chatbots can mimic human conversation dialogues, they are limited in social engagement, emotional expression, rapport building and personalisation.

Virtual Humans

Virtual humans are a form of embodied conversational agents that extend the capabilities of chatbots with their additional virtual embodiment and multimodal communicative capabilities that accompany the conversational agent (Cassell et al., 2000). Virtual humans have a computer-generated dialogue system and use multimodal communication cues to interact with people, while an animated face or body is presented on the screen. The addition of the virtual embodiment provides a more humanistic way of communicating and delivering health information or health interventions than conversational agents alone. The virtual embodiment can range from basic cartoons and animated characters to avatar with more advanced computer-generated imagery (CGI), such as Digital Humans, a type of virtual human developed by Soul Machines (Ltd). Depending on the virtual human's technical capabilities, they can be passive (i.e., delivering health information or self-help activities) or more interactive (i.e., delivering health interventions).

Virtual Human Benefits

This section describes some of the benefits of virtual humans in delivering e-Health interventions, including their accessibility, provision of health information, and ability to facilitate disclosure and develop rapport. Virtual humans are highly accessible, cost-effective, and scalable platforms, given that they only require an internet connection to use. The extent to which people use the internet has increased by 800 million in 2021, a 17% increase from pre-pandemic (ITU, 2021). The increasing amount of people who have access to an internet connection means that virtual humans are accessible to a greater number of patients around the clock on a range of devices (i.e., patients can use any device with an internet connection). This feature means that virtual humans may be able to reach populations who previously had limited access to traditional healthcare (e.g., those living rurally, working, or isolated during the pandemic) and be a convenient option to augment healthcare delivery (Griffiths et al., 2006).

Health literacy, the ability to understand basic health information, is vital in making medical decisions and giving informed consent to treatment (Ratzan & Parker, 2000). While health information is readily available on the internet, individuals with poor health literacy may struggle to find, understand, and evaluate the credibility of this information (Diviani et al., 2015). Virtual humans may help overcome health literacy barriers by providing an accessible way to deliver or present health information, especially when human support is not always available. For example, virtual humans have shown comparative effects to a human in explaining health documents for an informed consent procedure to participants with poor health literacy (Bickmore et al., 2009). Participants positively favoured virtual humans because they had no time constraints, could clarify information and were free from judgment and bias. Virtual humans have also extended their use into more disadvantaged populations, where there are disparities in health literacy. For example, the Spanish-language Virtual Patient Educator (VPE) is a virtual human that has been designed to address the disparities in healthcare communication, literacy, and knowledge for Hispanic women in a rural communities. The authors found that culturally tailoring the virtual human features (e.g., spoken language or avatar characteristics) contributed to greater understanding and trustworthiness. This study highlights the importance of tailoring and personalisation for virtual humans in their acceptability and effectiveness.

Virtual humans can also facilitate disclosure and honest responses in patients. Stigma, impression management, and fear of judgment can prevent patients from seeking help or reporting symptoms (Knaak et al., 2017; Thornicroft et al., 2009). Withholding honest responses and symptoms can give an inaccurate representation of patients' health and medical history, significantly contributing to poorer health outcomes. Virtual humans may avoid the social caveats of human delivery through their perceived anonymity and automatic nature. One study manipulated the framing of virtual humans as either computer administrated (i.e., a human is not watching or controlling the interaction) or human administrated (i.e., a human watching and controlling the interaction). The findings demonstrate that when virtual humans are described as automatic, patients are more likely to perceive the interaction as anonymous and free from the judgement or negative evaluations typically associated with human interactions (Lucas et al., 2014; Weisband & Kiesler, 1996). Other studies have found that individuals who interacted with virtual humans have reported feeling more comfortable disclosing sensitive information than their human counterparts (DeVault et al., 2014; Gratch et al., 2007) but preferred to interact with a human when discussing less sensitive information (Pickard et al., 2016). The anonymity of virtual humans may therefore be beneficial for extending the provision of healthcare to more stigmatised and otherwise harder to reach populations.

Due to their ability to engage in verbal and non-verbal behaviours, virtual humans can build rapport and patient-provider relationships. An essential part of healthcare is the communication and relationship between healthcare providers and their patients, with successful interactions linked with improved health outcomes (Chipidza et al., 2015), increased disclosure (Bickmore et al., 2005), and engagement in health care (Alexander et al., 2012). Rapport is a necessary factor in the establishment and sustainment of the therapeutic relationship and can be created by both verbal (e.g., more attentive or using follow up questions) and non-verbal behaviours (e.g., facial expressions, eye gaze or gestures; Burgoon et al., 2011; Miller et al., 1983). Combining verbal and non-verbal behaviours may help virtual humans stand apart from chatbots and passive mobile apps by creating and sustaining rapport with patients (Loveys et al., 2020). The virtual embodiment of virtual humans allows them to display non-verbal behaviours such as affiliative eye contact (sustained eye contact with the user; Pejsa et al., 2015) or multimodal emotional expression (Cerekovic et al., 2014; 2016; Loveys et al., 2020). Rapport can also be built when virtual humans engage in verbal behaviours such as using humour (Kulms et al., 2014), self-disclosure (Kang et al., 2012), storytelling (Gilani et al., 2016) and cooperative behaviours (i.e., working with the user on a shared goal; Kulms et al., 2014).

The combination of nonverbal and verbal behaviours (compared to displaying no relational cues) has also shown positive effects on relationship quality, social closeness, and working alliance (Bickmore et al., 2005; 2011; 2013; Loveys et al., 2020). A sense of social presence from interacting with a virtual human is associated with improved engagement (Heerink et al., 2012; Schuetzler et al., 2018). A virtual human may combine the benefits of computer-administered anonymity with rapport building similar to an actual human to facilitate disclosure, engagement, and improve health outcomes. However, despite these benefits, it is good to note that virtual humans are not designed to replace healthcare professionals but instead supplement and augment traditional healthcare.

Factors to Consider

It is necessary to consider how virtual humans' very human-like appearance, voice, and behaviour may affect patient interactions. The acceptance and real-world uptake of virtual humans may, in part, depend on the virtual human's realism. This section outlines issues to consider when using virtual humans to deliver health interventions, including the Uncanny Valley, the confidentiality of health information, ethical considerations, and deception.

According to the Uncanny Valley theory, people tend to view artificial agents and robots more positively as they become human-like, only up to a certain point (Mori et al., 1970; 2012). At this point, agents' perceptions can suddenly become negative, disgusted, and even distrustful. This effect often occurs when realism is high, with the presence of an abnormal feature. For example, when people interact with a realistic artificial agent, they may notice an abnormal or non-human like feature (e.g., a robotic voice or mismatch in lip-syncing) and experience eeriness and uneasiness. Fortunately, acceptance may be regained on the other side of the valley by balancing appearance realism with behavioural realism, but design limitations can often make this challenging (Bailenson et al., 2005; Garau et al., 2003). A qualitative study investigated the effects of virtual human design features on relationship quality, finding that people did not report feelings of eeriness or creepiness, suggesting that virtual humans, in that context, were able to avoid the uncanny valley. Including measures of acceptability and satisfaction, along with open-ended questions regarding their appearance and behaviour, provides feedback to shape the development and improvements of virtual humans in healthcare contexts (Sebastian & Richards, 2017; van Gemert-Pijnen et al., 2011).

As new technologies, such as virtual humans, are developed and integrated into healthcare, confidentially, storage and privacy are essential factors to consider. Health and psychological information are personal and sensitive, and patients expect their information to be kept confidential and private (Dong et al., 2011). Virtual humans can collect audiovisual data to interact and respond to users in real-time, so it is essential to consider how this information is stored or used after the interaction. Displaying a clear intention of data privacy, confidentiality, anonymity, and transparency around use for research should also be present (Kretzschmar et al., 2019).

When implementing virtual humans into healthcare settings, there are also ethical considerations to keep in mind. Interacting with virtual humans can mimic face to face conversations with health professionals, so managing attachment and deception are key. As discussed, the ability of patients to form social and close relationships with virtual humans can improve rapport and relationship quality. However, like other companion robots, patients may form attachments to the virtual human if used for more extended periods (Moyle et al., 2014). Attachment and possible negative feelings following the removal of the technology is a factor that needs to be considered when implementing virtual humans in healthcare settings, particularly for extended periods of use.

Additionally, avoiding deception is of utmost importance as patients need to be informed that a virtual human is not a real person (Loveys et al., 2020). This consideration is particularly relevant when using virtual humans with more vulnerable populations, such as those with dementia or psychosis (Bickmore et al., 2018). As the CGI technology develops and becomes more human-like, being transparent with its function and capabilities can help to minimise the risk of harm.

Virtual Human Health Applications

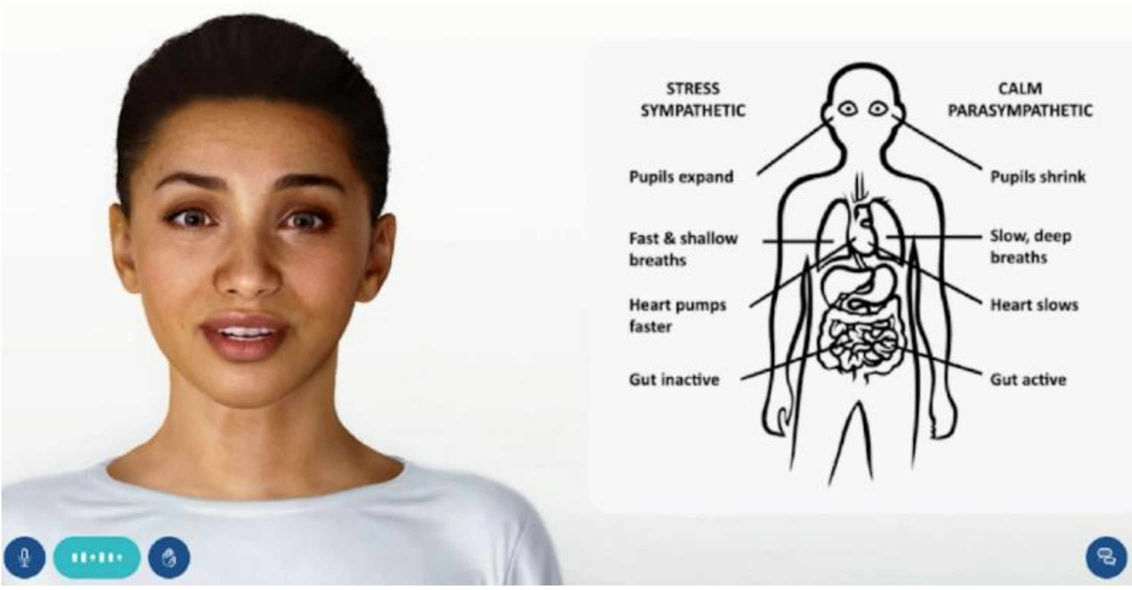
Depending on their technological capabilities, virtual humans can be designed to deliver a range of health and mental health interventions or information. Virtual humans, in a more passive role, can support health practitioners in diagnosing mental health disorders and collecting data. When used as a diagnostic tool, virtual humans were found to be valid and standardised in the identification of major depressive disorders symptoms (Philip et al., 2017) and produce high specificity and sensitivity in the Epworth Sleepiness Scale (ESS) in patients with obstructive sleep apnea (Philip et al., 2014). Patients with Post Traumatic Stress Disorder (PTSD) reported more symptoms when interviewed by the virtual human than an anonymised version of the Post-Deployment Health Assessment symptom checklist. This finding indicates that the virtual human could detect individuals who would have otherwise not been picked up or recognised as fulfilling the PTSD diagnosis (Lucas et al., 2017), highlighting their potential ability to work with more stigmatised populations and contexts.

The interactive capabilities of virtual humans may allow them to deliver healthcare information and interventions, with a growing body of literature demonstrating their feasibility and acceptability. A virtual coach was feasible and more effective in establishing a regular practice, improving self-efficacy, and advancing in change stages in a mindfulness program compared to self-administration using audio and written material (Hudlicka, 2013). A virtual human has delivered information about healthy lifestyle behaviours to an ethnically diverse sample of women, such as physical activity, healthy eating, mindfulness, and stress management techniques. Although there were significant reductions in alcohol intake and increases in fruit consumption, this study was not adequately powered, so the effectiveness in reducing stress was not determined (Gardiner et al., 2017). Other studies have shown that virtual medical agents are feasible for conducting medical interviews (Micoulaud-Franchi et al., 2016) and facilitating disclosure and empathy in patients with mental disorders, such as depression (Philip et al., 2017), and tobacco and alcohol use disorders (Auriacombe et al., 2018). These findings illustrate promising evidence that virtual humans may be feasible to deliver stress and lifestyle information and conduct medical interviewing.

Two recent feasibility studies using Digital Humans (a type of virtual human developed by Soul Machines) add to the promising evidence base, as presented below. The first study found that a Digital Human was feasible and acceptable in delivering a remote loneliness intervention to adults at risk of developing severe COVID-19. Younger adults with health conditions and older adults living independently found the Digital Human easier to use than those living in a nursing home who required external assistance from a caregiver (Loveys et al., 2021).

A second pilot study found that Digital Humans could feasibly and acceptably deliver Cognitive Stress Management (CSBM) exercises, with results comparable to the same content delivered by a teletherapist and a digital manual. The CSBM program included information and cognitive exercises to improve stress awareness (see Figure 1 for an example), psychoeducation on the benefits of deep breathing and a deep breathing exercise (human audiotape). Both the Digital Human and a human teletherapist received positive ratings, but the teletherapist received the highest rapport and trust ratings. Exploratory analyses found significant positive effects of the intervention on psychological stress, loneliness, HR, and EDA, with large effect sizes. However, the study was not powered to find significant effects, and an RCT is needed to explore their ability to improve health outcomes and psychological well-being.

Figure 1.
The Digital Human interface ("Bella") delivering psychoeducation about the stress and relaxation responses



Note: Reprinted with permission from (Loveys et al., 2021)

Summary

This chapter has argued for eHealth and mHealth technologies to improve the reach, access and convenience of health interventions and information. Artificial agents have been shaping the path in the eHealth space in the last decade, with virtual humans emerging as a novel platform. The CGI virtual embodiment, ease of access, and multimodal emotional expression of virtual humans are beneficial features for healthcare, but the Uncanny Valley and ethics must be equally considered in their healthcare applications. Two pilot studies show the acceptability and feasibility of using Digital Humans for delivering psychological interventions in health contexts. The next step is to investigate their effectiveness on health outcomes in an RCT.

Chapter II: Wound Healing and Stress

Introduction

This thesis describes an RCT conducted to examine the effects of a relaxation intervention delivered by a virtual human on psychological outcomes and wound healing, compared to the same intervention delivered by a human recorded audiotape and reading magazines (control condition). Wound healing was chosen as an outcome because it reflects the functioning of the immune system, is clinically relevant, and is negatively affected by psychological stress. Previous studies have shown that relaxation interventions can improve wound healing when delivered by a human therapist or audio recordings from a real human. The following chapter places the study in the context of wound healing by introducing the clinical importance of wound healing, describing the healing process, and outlining how psychological stress can affect healing. It also describes evidence to date for the detrimental effects of stress on healing.

The Clinical Importance of Wound Healing

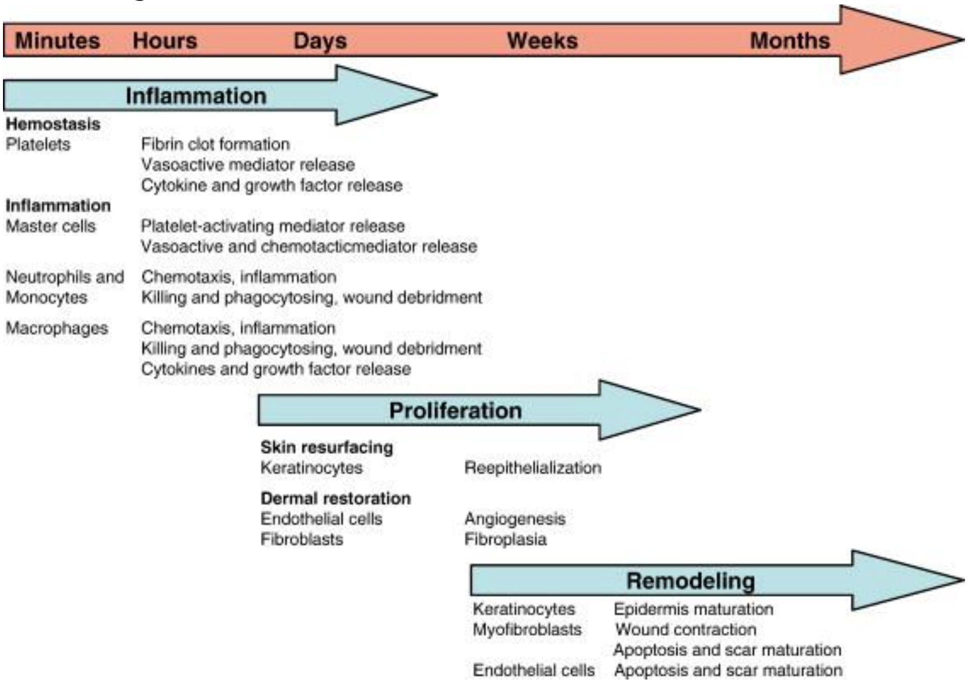
A wound is formed when the anatomical structure and function of the skin are disrupted or damaged (Velnar et al., 2009). The skin plays an essential role in protecting the body against bacteria, viruses, and antigens while controlling water movement in and out of the body and maintaining homeostasis (Enoch & Leaper, 2007; Marks, 2004). The skin acts as the central defensive mechanism for the immune system, and good health relies on the skin's ability to recover after tissue damage or disruption (Christian et al., 2006).

When the skin cannot recover and repair itself in an appropriate amount of time, serious complications can follow (e.g., non-healing and chronic wounds, poor healing, or uncontrolled healing; Basu & Shukla, 2012). Acute wounds that are not managed appropriately or where the healing process is disrupted and deregulated can result in longer healing times and may progress into chronic wounds (Eming et al., 2014; Velnar et al., 2009). Poor wound healing and unhealed, chronic wounds directly affect patients by increasing their risk of infection, discomfort, morbidity, and mortality (Gouin & Kiecolt-Glaser, 2011). Not only are there direct patient impacts, but poor wound healing can also put extra strain on the healthcare system by increasing the length of hospital stays and healthcare costs (Broadbent et al., 2003; Guo & DiPetro, 2010; Robinson et al., 2017). Therefore, wound healing is a clinically relevant outcome that indicates health, wound management, and immune functioning.

The Wound Healing Process

Wound healing is a continuous process that can be broken down into a cascade of dynamic and overlapping stages; haemostasis, inflammation, proliferation, and remodelling (Christian et al., 2006; Li et al., 2007; Velnar et al., 2009). Figure 2 illustrates the overlapping timeframes for each stage and demonstrates the complex interactions between stages and cells involved during wound healing. Immediately after injury, the clotting cascade is activated, and haemostasis begins. This stage protects the vascular system, ensuring that, despite the injury, vital organs can still function. Reaching haemostasis usually takes a few hours to complete and involves a series of vasoconstriction, coagulation, platelet aggregation, and clot formation (Li et al., 2007; Velnar et al., 2009). The resulting blood clot comprises fibronectin, fibrin, vitronectin, and thrombospondin, preventing further blood loss. The clot also acts as a temporary extracellular matrix for later cell migration (Li et al., 2007; Natarajan et al., 2013). Platelets in the clot begin releasing growth factors and chemokines, which activate and attract more immune cells (such as neutrophils, macrophages, endothelial cells, and fibroblasts) into the wound site, activating the inflammatory response of the next stage (Li et al., 2007; Velnar et al., 2009).

Figure 2.
Diagram showing the overlapping stages of wound healing over time and the substages and cells involved



Note: reprinted with permission from (Li et al., 2007)

The role of the inflammatory stage is to protect the wound site from bacteria and prevent further tissue damage before preparing the wound for repair. The immune cells prominently involved in this phase are neutrophils and macrophages, which have phagocytic roles (ingesting foreign matter; Christian et al., 2006; Lawrence & Diegel, 1994). Neutrophils are drawn into the wound site and dominate the early inflammatory response by destroying and removing bacteria and damaged tissue (Broughton et al., 2006; Tsirogianni et al., 2006; Velnar et al., 2006). Once bacteria are removed from the wound, neutrophils are taken away by the escar or ingested by macrophages, while macrophages continue phagocytosis (Aderem, 2003). Macrophages express signalling receptors, such as toll-like receptors (TLR), which act as protein recognition receptors that bind to foreign substances and activate cellular pathways (Tsirogianni et al., 2006). These receptors trigger the signalling pathway and activate transcription factors, such as nuclear factor-kB (NF-κB). NF-κB moves into the cell nucleus to produce inflammatory mediators such as chemokines, adhesion molecules, growth factors and proinflammatory cytokines (i.e., necrosis factor-α (TNF-α) and interleukin-1). Additionally, IL-1 and TNF- α receptors can activate the transcription of (NF-κB), further enhancing the immune response.

The inflammatory mediators (such as TNF-α and IL-1) are communicative molecules that attract leukocytes and other skin cells into the wound, beginning the adaptive immune response and coordinating the start of tissue repair (Christian et al., 2006; Li et al., 2007; Tsirogianni et al., 2006). The inflammatory phase cleans the wound of foreign debris and bacteria while preparing the wound for repair, which typically lasts between one and five days (Velnar et al., 2009). When this phase is disrupted and delayed longer than two weeks, the wound becomes a state of chronic inflammation (Li et al., 2007).

The proliferative phase begins a few days later to repair the wound site and build up tissue again after the injury (Broughton et al., 2006). This phase is dominated by cellular activity, and three key events occur re-epithelisation, angiogenesis, and fibroplasia. Re-epithelialisation is the repair of injured tissue and permeability barrier where keratinocytes migrate into the wound and proliferate to reform the basement membrane zone (the connection between the epidermis and dermis underneath; Li et al., 2007). If re-epithelialisation is unsuccessful or delayed, the wound site will remain open and susceptible to further infection (Sivamani et al., 2009). The temporary extracellular matrix formed earlier in the healing process is used as a scaffold for angiogenesis and fibroplasia to replace the injured dermal tissue (Gurtner et al., 2008; Li et al., 2007; Romana-Souza et al., 2010). Creating new blood vessels (angiogenesis) and the migration, proliferation of fibroblasts and production of matrix proteins (fibroplasia) work together to create granulation tissue to reconstruct the dermis (Christian et al., 2006; Li et al., 2007).

The final stage of the healing process is remodelling, which involves wound contraction, extracellular matrix reorganisation and scar formation. Fibroblasts differentiate into myofibroblasts which have contractive features that allow the tissue to close together (Gurtner et al., 2008; Tsirogianni et al., 2006). Matrix metalloproteinases (MMPs) are released by immune cells and regulate the collagen fibres to reorganise the extracellular matrix (Cole-King et al., 2001). The fibrin clot created in haemostasis and replaced during proliferation by collagen-rich granulation tissue and blood vessels now remodel into a collagenous scar. Too much collagen can create a hypertrophic scar or keloid, whereas not enough collagen (due to deposition problems) can result in a very weakly healed wound (Broughton et al., 2006). The remodelling phase usually takes a few weeks but can be extended to years after the initial injury (Christian et al., 2006). While slightly different to the previous skin, the healed wound now has a similar structure and functionality (Li et al., 2007; Velnar et al., 2009)

The length and success of healing depend heavily on the immune functioning and regulation at each stage (Guo & DiPetro, 2010; Hübner et al., 1996), where succession to the next stage depends on the success of the prior stage. With healthy immune functioning and regulated immune responses, wounds heal within a reasonable time frame and are less likely to become infected (Cole-King et al., 2001). However, when the immune response becomes dysregulated or impaired at any phase in the healing process, the wound can become infected and unhealed.

Types of Wounds

Experimental wounds (including tape-stripping, punch biopsies, and suction blisters) are standardised and tested in a controlled environment and are often used to isolate contributing factors (i.e., stress), investigate specific underlying pathways (i.e., stress reduction) or test interventions (i.e., stress reduction interventions; Marks, 2004). For example, tape-stripping is a non-invasive, inexpensive, and quick way to model wound healing by creating a minor disruption to the epidermis (Marks, 2004; Walburn et al., 2009). This disruption triggers the wound healing cascade whereby the immune system responds and works to repair the damage to the skin barrier (Maarouf et al., 2019). On the other hand, clinical wounds (e.g., chronic, or surgical wounds) are more significant and reflective of the wound healing process and patient experiences (Walburn et al., 2009). Often testing is done with experimental wounds (such as tape-stripping) before translating to clinical wound and patient samples (Gouin & Kiecolt-Glaser, 2011).

Influence of Stress on Wound Healing

As described above, wound healing involves complex and overlapping stages that rely on regulated and functioning immune responses. Factors that can influence immune regulation and functioning may modulate the wound healing process. The immune system, which was once regarded as self-regulative and autonomous, is now considered interrelated with the nervous system and psychological processes (Christian et al., 2006; Padgett & Glaser, 2003). The shift to a psychoneuroimmunological framework theorises that psychological factors, such as stress, can work through direct neuroendocrine or indirect health behaviour pathways to influence immune activity (Kiecolt-Glaser et al., 1995). As a result, research suggests that stress can slow healing. A meta-analysis showed that 17 of the 22 studies found that stress impaired wound healing across different stress and wound types or resulted in a downregulation of healing biomarkers (Walburn et al., 2009). It also demonstrated that various forms of stress affect experimental and clinical wounds, including general life stress (perceived stress), caregiving, examination, marriage, and experimentally induced. The following section defines stress, explores the proposed mechanisms behind this effect and reviews the evidence for these.

What is Stress?

Psychological stress develops when demands and environmental stimuli overpower a person's perceived ability to cope (Cohen et al., 1997). Stress can be described as three moving parts;

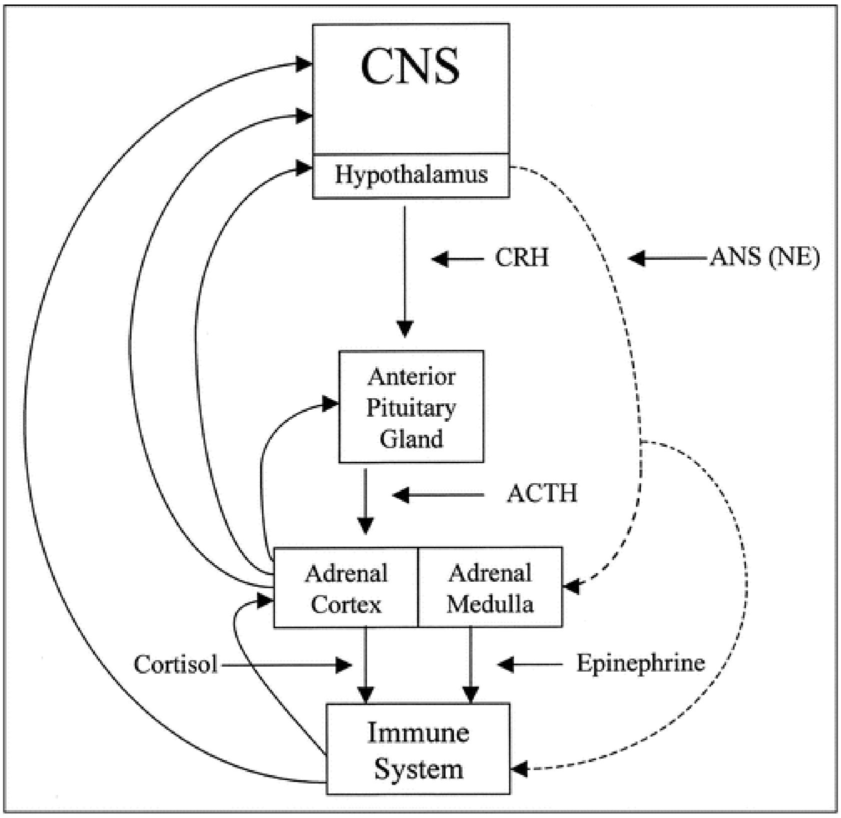
the environmental stimuli (i.e., stressors), the brain perceiving the stressor or inability to cope (stress perception), and the physiological response in the body to deal with it accordingly (stress response; Dhabhar et al., 2019). Evidence suggests that prolonged or chronic psychological stress is related to poorer health outcomes, suppressed immune functioning, and impaired wound healing (Guo & DiPietro, 2010; Segerstrom & Miller, 2004; Walburn et al., 2009). Given the prevalence of stress (recently exacerbated during the COVID-19 pandemic; Salari et al., 2020) and the adverse effects of prolonged exposure, understanding the underlying mechanisms and how to mitigate these effects is essential for future research.

The Stress Response

The autonomic nervous system (ANS) is comprised of two moving subsystems: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), which work in balance to keep the body at homeostasis (Kemeny, 2003). When the body perceives stress (i.e., threats to the system), the SNS responds by activating the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adreno-medullar (SAM) axis. These axes release neurotransmitters and endocrine hormones to respond to the stressor and provide energy to parts of the body that need them most (Dusek & Benson, 2009).

The SAM axis is responsible for the initial fight or flight response by releasing catecholamines norepinephrine (NE) and epinephrine from the adrenal medulla (see Figure 3) into the bloodstream. As NE and epinephrine directly innerve the body’s organs (such as skeletal muscles, lungs, heart), the body can respond to the stressor immediately. This fight or flight response is exhibited through excitatory physiological behaviours such as increased HR, EDA, blood pressure, rapid breathing, and dilating pupils.

Figure 3.
Illustration of the cascading effects following a stressor on the HPA and SAM axes



Note: Reprinted with permission from (Kemeny, 2003).

Once the SAM axis response slows down, the HPA axis (endocrine stress response) takes over. The hypothalamus releases corticotropin-releasing factor (CRF) into the anterior pituitary, triggering the release of adrenocorticotropic hormone (ACTH; see Figure 3). Once in the bloodstream, ACTH activates the release of glucocorticoids (such as cortisol) from the adrenal cortex, which are used for energy by the brain, metabolism, cardiovascular and renal function, and the inflammatory response to help work against the stressor (Padgett & Glaser, 2003). These glucocorticoids can then modulate the immune system and its response by influencing immune cell trafficking and cytokine expression (Vileikyte, 2007). The PNS then works to reverse the SNS activation by calming the body down after the stressor and engaging in resting functions (e.g., slowing the heartbeat, decreasing EDA, constricting pupils) to ensure the body returns to homeostasis (Kemeny, 2003).

Direct Mechanisms of Stress

The literature suggests that stress likely modulates healing through two possible direct mechanisms; the HPA and SAM axes and indirectly through health behaviours (O'Connor et al., 2020). Under acute stress, activated HPA and SAM axes are adaptive and enhance wound healing, but if activated for extended periods of stress, they have maladaptive effects that can dysregulate immune functioning and slow healing (Segerstrom & Miller, 2004). The following section presents the three mechanisms and evidence illustrating these.

HPA Pathway

As part of the nervous system, the neuroendocrine system is the first proposed direct pathway for stress to influence the immune response and wound healing. During acute stress, increases in glucocorticoids (such as cortisol) enhance immune functioning by drawing more immune cells to the wound site, resulting in faster wound healing (Dhabhar, 2006; 2019).

However, chronic activation of the HPA axis during chronic stress may have suppressive and dysregulating effects on the immune system (Dhabhar, 2006; Heijnen, 2007). Lymphocytes and other immune cells (such as neutrophils and macrophages) have receptors that recognise neurotransmitter and endocrine hormone signals (Heijnen, 2007). The receptors can interfere with and activate these signals, modulating immune activity such as cytokine secretion, cellular trafficking, and antibody production (Ader, 2000; Padgett & Glaser, 2003). Heightened glucocorticoid levels may reduce the number of circulating proinflammatory cytokines and growth factors available to regulate tissue oxygenation, proliferation, collagen synthesis, phagocytosis, and wound bed clearance. The cascading effects from these disturbances prolong and impair the wound healing process and increase the risk of infections (Glaser et al., 1999; Kiecolt-Glaser et al., 2005; Li et al., 2007).

Experimental studies have shown these associations between poor healing, self-reported stress, and stress biomarkers. Sleep deprivation and interview stress delayed SBR and were associated with increases in cortisol, proinflammatory cytokines (IL-1β and IL-10), and natural killer cell activity (Altemus et al., 2001). Exam stress has reportedly slowed punch biopsy wounds by 40% longer and resulted in a lower production of IL-1 levels (Marucha et al., 1998). In couples with blister wounds, marital stress was associated with slower healing and lower local cytokine production (plasma IL-6 and TNF-alpha) at the wound site compared to their less-stressed counterparts who had social support interactions (Kiecolt-Glaser et al., 2005).

As expected, higher self-reported perceived stress levels have been shown to correlate with slower healing of punch biopsy, blister wounds and inguinal hernia, as well as higher cortisol (Ebrecht et al., 2004; Glaser et al., 1999), lower IL-1β levels (Broadbent et al., 2003; Kiecolt-Glaser et al., 1995), and lower IL-1α and IL-8 counts (Glaser et al., 1999). Future research should continue measuring stress biomarkers, such as cortisol, as well as including a measure of self-reported stress to replicate these findings and further the understanding of the underlying mechanisms (Gruzelier, 2002).

SAM Pathway

The second proposed direct mechanism is the SAM axis, whereby autonomic innervation of lymphoid tissue links psychological stress with the immune system and wound healing responses, as evidenced by stress biomarkers. The nervous system is connected to the primary (i.e., bone marrow) and secondary (i.e., lymph nodes) lymphoid tissues via sympathetic nerve fibres (Felten & Felten, 1994). The terminal of these fibres neighbour immune cells, which have adrenergic receptors. Neurotransmitters NE and epinephrine can directly bind onto the immune cells through these receptors, modulating immune activity and healing (Felten et al., 1985; Sanders & Kohm, 2002).

An example of this immune modulation and dysregulation is the effect on the healing process observed in heightened epinephrine levels as a response to increased psychological stress. Chronically increased epinephrine levels during wound healing can alter keratinocyte and fibroblast activity and prolong re-epithelisation and granulation tissue formation during the proliferation stage (Maarouf et al., 2019). For example, one of the most important receptors for the immune system is β2-adrenergic receptors (β2AR), and research has found links between these receptors and wound healing (Madden, 2003). Keratinocytes and fibroblasts express β2ARs which become activated when systemic or local epinephrine levels increase due to psychological stress. Activated receptors on keratinocytes can reduce migratory pathways, preventing keratinocytes from migrating independently and re-epithelising, delaying the proliferative stage of wound healing (Sivamani et al., 2009; Steenhuis et al., 2011). Moreover, wound healing has been improved using β2-AR blockades as receptor-specific antagonists (Ghoghawala et al., 2008; Pullar et al., 2006). Activation of β2ARs on fibroblasts can increase fibroblast proliferation and myofibroblast differentiation but limit fibroblast migration and collagen deposition (Romana-Souza et al., 2009; 2011). These fibroblast alterations can prolong the granulation tissue formation phase, delaying wound proliferation and closure (Maarouf et al., 2019).

Traditionally, studies measure NE or epinephrine levels to monitor SNS activity, but a less invasive biomarker, salivary alpha-amylase (sAA), may be appropriate. Increases in catecholamines during a stress response through activation of the SAM can stimulate and alter salivary gland receptor activity, including the enzyme sAA (Granger et al., 2007; Nater & Rohleder, 2009; Piazza et al., 2010). As sAA follows NE activity by ten minutes, it makes an alternative biomarker that parallels the NE response to measure SAM activation (Rohleder et al., 2004).

Indirect Mechanisms of Stress

Stress may also indirectly impair healing through health behaviours. Individuals with lower psychological well-being and higher levels of distress are more likely to engage in unhealthy behaviours and habits such as poor sleep and diet, substance use (alcohol or drugs), smoking (Kiecolt-Glaser & Glaser, 1988), and not adhering to medication (Robinson et al., 2017). These unhealthy behaviours may deregulate the immune response, subsequently impairing the healing response (Guo & DiPietro, 2010).

Evidence to date shows that poor sleep behaviours have consistently been linked with poor immune functioning and impaired wound healing. Deep sleep can trigger the release of growth hormones that act to enhance immune functioning (Veldhuis & Iranmanesch, 1988); while poor sleep, sleepiness and fatigue during the day are associated with higher levels of cortisol and proinflammatory cytokines, such as IL-6 (Leproult et al., 1997; Vgontzas et al., 1999). For example, sleep deprivation has been linked with slower SBR and increased activity of natural killer cells, plasma interleukin-1β, and tumour necrosis factor-α after a tape-stripping wound (Altemus et al., 2001). Moreover, poor sleep may exacerbate distress and further deregulate the immune response (House, 2015). Therefore, through modulation of immune function, poor sleep behaviour may impair wound healing (Irwin, 2007).

Alternatively, positive health behaviours (such as exercise) have been associated with improved healing. Mice who exercised on a wheel for 30 minutes a day had faster cutaneous healing from a dermal wound and smaller wound sizes than a control group who were not provided with an exercise wheel. The levels of TNF-α, keratinocyte chemoattractant and monocyte chemoattractant protein-1 were lower in the exercise group, suggesting an anti-inflammatory response from the exercise (Keylock et al., 2008). These effects also translate to humans. For example, older adults who engaged in regular exercise in a four-week program had a 25% faster healing rate than participants who did not exercise. Those who exercised also displayed enhanced neuroendocrine reactivity, and the authors attribute the enhanced healing to work through these neuroendocrine regulation pathways (Emery et al., 2005).

Other health behaviours such as smoking, alcohol, and diet have mixed evidence for their effect on wound healing. Studies have found associations between individuals who smoke and higher levels of IL-6 and CRP (Taaffe et al., 2000) and impaired healing of the diabetic foot (Monami et al., 2008). Nicotine is a vasoconstrictor (reduces blood flow) that can increase platelets' adhesiveness, reduce the proliferation of blood and immune cells, and inhibit epithelisation (Sherwin & Gastwirth, 1990; Silverstein, 1992). Through this, the wound healing process can become impaired and dysregulated. However, some studies have shown that other health behaviours such as drinking caffeine (Marucha et al., 1998), alcohol consumption, healthy eating, and sleep (Ebrecht et al., 2004) were not linked with healing or cytokine levels (Glaser, 1999). Given the mixed results, health behaviours warrant further investigation. The current study used a health behaviour questionnaire at baseline to investigate some of these health behaviours as an indirect pathway through which psychological stress may influence wound healing.

Summary

Together, the evidence indicates that psychological stress and the cascading stress response can alter immune functioning and impair wound healing. Given the immune system's role in the healing process, wound healing is an outcome measure that reflects health, wound management, and immune functioning. The studies described in the section above have illustrated three theorised mechanisms through which stress can impair healing, but due to the complex interplay between healing, immune and stress parameters, there is still insufficient evidence to understand these mechanisms fully.

Despite this, the robust evidence demonstrating that stress impairs wound healing highlights the importance of managing psychological stress to prevent complications related to poor healing. Using experimental and standardised wounds, such as tape-stripping, in healthy populations provides a controlled environment to test design and delivery factors before translating these interventions to clinical populations.

The next chapter introduces relaxation as a stress reduction intervention. It describes evidence from several trials that relaxation exercises can improve healing for both experimental and clinical wounds. The chapter outlines a gap in the current literature on whether a virtual human can deliver a relaxation intervention to reduce stress and improve wound healing with comparable effects to traditional relaxation delivery methods.

Chapter III: Relaxation

The previous chapters have argued that virtual humans may be useful in delivering stress management interventions and improving health outcomes in a healthcare system that does not have enough resources to meet current needs. They have also outlined the importance of RCTs in establishing that virtual humans are an effective delivery method. It has been argued that a good testbed for this is the study of relaxation interventions and their effects on wound healing.

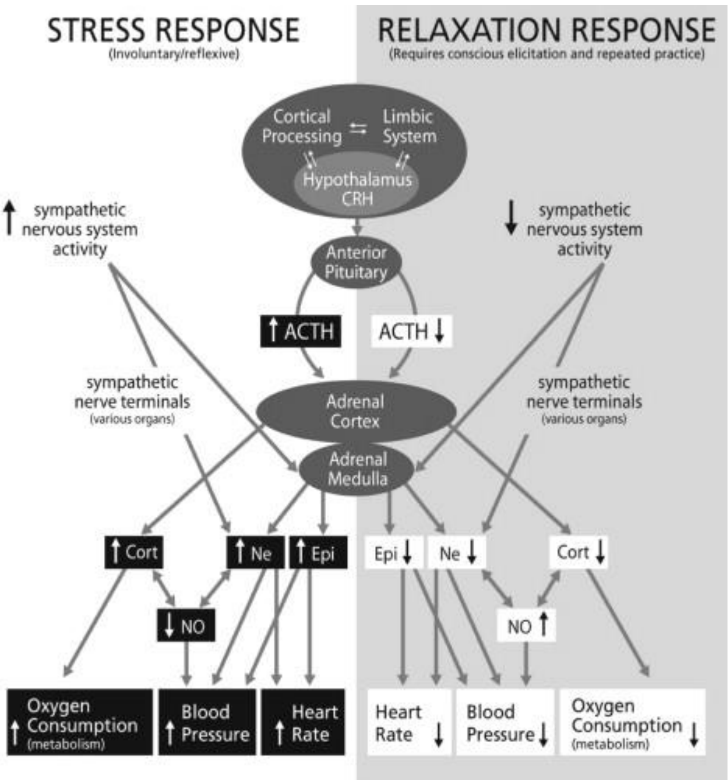
There is some evidence that chatbots and other virtual humans may reduce stress through stress management skills (Gaffney et al., 2014; Loveys et al., 2021; 2022; Ly et al., 2017) and education (Gardiner et al., 2017; Hudlicka, 2013) but no studies have investigated their role in delivering relaxation interventions, compared to a simple human recorded audiotape. Virtual humans have a unique ability to hold more complex conversations with patients and deliver healthcare information, but their ability to effectively relax people is unclear. Their computer-generated voice and face may impact their ability to induce a relaxation response. The current RCT investigates their ability to reduce stress, induce the relaxation response, and improve wound healing, contributing a novel application to the computer agent literature.

This chapter describes the relaxation response and the mechanisms by which it can affect healing. Different types of relaxation techniques are described, and evidence for their effects on self-reported stress and the physiological stress response. This is followed by a section specifically examining their effects on wound healing.

The Relaxation Response

Relaxation interventions are theorised to induce the relaxation response that can counterbalance the reflexive stress response by reducing sympathetic activation and increasing parasympathetic activity (Benson et al., 1974; Cohen et al., 2007; Wahbeh et al., 2012). As seen in Figure 4, the relaxation response is a physiological state characteristic of reduced SNS arousal and physiological behaviours that oppose the stress response (Dusek & Benson, 2009; Park et al., 2013). The relaxation response is induced when the trophotropic zone (anterior area of the hypothalamus) is stimulated voluntarily, often through specific mind-body relaxation techniques. This stimulation can reduce SNS arousal, slowing down the release of corticosteroids and glucocorticoids from the HPA and SAM axis. As a result, the PNS takes over to counterbalance the increased sympathetic activity during the stress response and restore balance to the ANS.

Figure 4.
Diagram showing opposing stress and relaxation responses



Note: Reprinted with permission from (Dusek & Benson, 2009)

The ANS is dominated by parasympathetic activity during the relaxation response state, while the SNS becomes less aroused (Smith, 2007). This shift between sympathetic to parasympathetic activity is often reflected in physiological responses such as a lower HR, blood pressure, respiratory rate, reduced EDA, reduced pupil constriction, reduction in oxygen consumption (slower metabolism) and carbon dioxide elimination (Dusek & Benson, 2009; Cohen & Miller, 2001; Wallace et al., 1971). These physiological changes can be described as a relaxed state.

Quantifying this shift between systems and the overall ANS activity can be measured by non-invasive wearable sensor watches that can collect real-time data, such as HR or EDA (Ahmed et al., 2015; Amin & Faghih, 2018; Nakao, 2019). An objective measure of autonomic activity can help determine whether parasympathetic activity (as opposed to sympathetic) dominates after relaxation.

Relaxation and Wound Healing Mechanism of Action

The rationale behind the relaxation response is that voluntarily inducing this physiological state can counterbalance and buffer against long term stress (i.e., chronic SNS arousal) and theoretically modulate immune responsiveness and improve wound healing (Pawlow & Jones, 2002). As the SNS becomes less aroused, the HPA and SAM slow down the release of corticosteroids and glucocorticoids, reducing the number of circulating stress hormones. As stress hormones can have an immunosuppressant effect on healing, reducing these may reverse the adverse effects and enhance healing (Holden-lund, 1988; Robinson et al., 2015). However, there is insufficient and mixed evidence for the mechanisms behind the relaxation response and the timeframe it works on the wound healing process, highlighting the need to include stress biomarkers to further test underlying pathways.

Relaxation Techniques

Relaxation techniques incorporate components necessary to elicit the relaxation response, as outlined above, and are often used in combination within a relaxation intervention. These techniques help counterbalance the stress response, reflected in decreases in sympathetic activity, measured by physiological outcomes (Smith, 2007). The following section outlines some common techniques, such as progressive muscle relaxation (PMR), deep breathing, guided imagery (GI), meditation, voice, and music, along with evidence showing their effects on physiological and psychological outcomes in a variety of health contexts.

Progressive Muscle Relaxation

PMR is a technique that involves systematically tensing and relaxing muscles around the body to counteract muscle tension associated with stress (Bernstein & Borkovec, 1973; Jacobs, 2001). One of the physiological changes associated with the stress response is muscle tension, leading to severe muscle pain and fatigue if chronically stressed. These physiological changes are also associated with greater perceived stress and anxiety (Park et al., 2013). PMR starts with tensing one muscle group (usually right arm and hand) for around five to seven seconds and focusing on this feeling of tension. After this, tension is released, and the focus should then shift to the feelings of the muscles being relaxed (McCallie et al., 2006). Bernstein and Borkovec (1973) suggest that after the right arm and hand, this technique should move around the body to the left arm and hand, the face, the shoulders and neck, the chest, back and abdomen, the right leg and finish with the left leg. Relaxing each muscle can provide immediate relief to the physiological tension of the muscles resulting from stress, while practising and distinguishing between states of tension and relaxation can help an individual notice an onset of stress-related muscle tension and counteract it with relaxation when needed (Conrad & Roth, 2007; Smith, 2007). This awareness can help block and relieve stress-related muscle tension and instead induce a state of physiological relaxation, further improving perceived stress and subjective anxiety (Esch et al., 2003; Park et al., 2013).

PMR is considered an effective technique for reducing anxiety symptoms, physiological arousal, and psychological stress in healthy participants. In a review of relaxation techniques, PMR had a large effect size and was considered an effective way to reduce psychological anxiety levels (Manzoni et al., 2008). A PMR intervention conducted twice (a week apart) resulted in significantly lower HR, state anxiety, sCort, perceived stress and relaxation levels than the control group (quiet sitting; Pawlow & Jones, 2002). Similar physiological effects were replicated in a more recent study that found that 20 minutes of listening to PMR exercises resulted in reduced EDA and HR and increased psychological relaxation states (Toussaint et al., 2021). However, this study did not measure psychological stress levels so is unclear whether 20 minutes was enough to reduce psychological stress, as well as relaxation levels.

PMR has also been applied to clinical health populations and has shown improvements in sleep quality and fatigue levels for individuals with rheumatoid arthritis (Kılıç & Parlar, 2021), pain symptoms for those with chronic back pain, arthritis and pregnancy-related pain (Dunford & Thompson, 2010; Kwekkeboom & Gretarsdottir, 2006), pain management in those with sickle cell anaemia (Kazak & Ozkaraman, 2021), depression and anxiety symptoms in cancer patients (Holland et al., 1991; Sloman & Hons, 2002) and HR and state anxiety in cardiac rehabilitation patients (Wilk & Turkoski, 2001). This evidence indicates that PMR can be an effective relaxation technique used in various health contexts to manage pain, anxiety, and stress symptoms and reduce sympathetic activity.

Deep breathing

Deep breathing, also known as diaphragmatic breathing, involves using the diaphragmatic muscles to breathe straight from the abdomen into the lungs to help restore balance to the ANS (Jerath et al., 2006). Part of the stress response is rapid breathing which can be adaptive in acutely stressful situations, but over time these shallow and rapid breathing patterns can create a vicious cycle of physiological tension and SNS arousal (Jerath et al., 2006; Smith, 2007). Deep breathing is a low-frequency respiration technique that deepens and lengthens the inhalation and exhalation at a rhythmic and even pace, decreasing the overall respiratory rates (Perciavalle et al., 2017). During deep breathing, the ANS shifts from high SNS arousal to a PNS-dominated response, inducing the relaxation response and restoring the balance between the two systems (Jerath et al., 2006). Doing this can normalise the cardio-respiratory system and, over time, can improve its ability to change oxygen into energy and remove waste (i.e., carbon dioxide; Gopal et al., 1973; Smith, 2007).

Deep breathing exercises have been associated with changes in physiological and psychological states and stress biomarkers, indicating reduced sympathetic activity. Studies have found that deep breathing exercises were associated with greater galvanic skin resistance (Telles & Nagendra, 1994), reduced oxygen consumption (Telles & Desiraju, 1991), HR and blood pressure (Perciavalle et al., 2017; Velkumary & Madanmohan, 2004). Psychological states have also improved because of deep breathing exercises, for example, improved perceived stress (Perciavalle et al., 2017; Warsono, 2020), mood (Perciavalle et al., 2017) and preoperative anxiety levels (Pardede et al., 2020). As theorised, these physiological changes have also been accompanied by reductions in stress biomarker changes, with cortisol (of the HPA axis) being the most documented (Ma et al., 2017; Perciavalle et al., 2017). Together, these studies support the stress reduction theory through which deep breathing induces the relaxation response to improve physiological and psychological outcomes with possible HPA mediation.

Guided Imagery

GI involves replacing distressing memories with healing and positive images and thoughts using imagination and visualisation (Achterberg, 1985; Naparstek, 1994; Park et al., 2013). Instructional guidance and sensory and patient contextual engagement enhance this process by creating more realistic mental representations and images. The theoretical basis behind GI is that because negative thoughts and memories can evoke physiological distress responses, shifting cognition and images to more positive and healing ones can alleviate physiological stress symptoms (Donaldson, 2000; Park et al., 2013; Smith, 2007).

Several studies in a range of healthy samples and healthcare settings support this theory, evidenced by reductions in anxiety and stress responses. GI has been associated with significant reductions in self-reported stress, relaxation and negative thoughts in healthy participants (Carter, 2006), reductions in anxiety with patients undergoing abdominal surgery experienced (Prabhaa & Joseph, 2020), reductions in preoperative anxiety and cortisol in bariatric surgery patients (Felix et al., 2018), reductions in death anxiety in nurses working during the COVID-19 pandemic (Sanadgol et al., 2020), reductions in systolic and diastolic blood pressure during pregnancy (Ali Far & Nokani, 2013), improvements in stress, fatigue and HRV in patients with thyroid cancer (Lee et al., 2013) and increases in psychological relaxation levels and decreased EDA in a healthy sample (Toussaint et al., 2021). Together, it appears that GI is an effective technique at inducing the relaxation response (as evidenced by reduced sympathetic activity and self-reported stress).

Meditation

Meditation is a technique that involves focusing attention and awareness to control mental processes (Walsh & Shapiro, 2006). This is often referred to as a "thoughtless awareness", where the activity of the mind reduces while keeping at a level of alertness (Kokoszka et al., 1990). In its various cultures and forms, meditation has been shown to effectively reduce physiological and psychological stress responses and stress biomarkers, indicating an ability to induce a relaxation response state (Ospina et al., 2007). Studies have shown meditation is associated with reductions in HR (Tang et al., 2009; Telles et al., 1998; Zou et al., 2018), blood pressure (Sudsuang et al., 1991; Wenneberg et al., 1997), perceived stress levels (Zou et al., 2018), respiratory rates and EDA (Tang et al., 2009; Telles et al., 1998; West, 1979).

In addition, meditation has also been associated with changes in stress biomarkers but may depend on moderating factors. For example, meditation has reduced levels of cortisol (Jevning et al., 1978; MacLean et al., 1997; Sudsuang et al., 1991; Vedamurthachar et al., 2006; Witek-Janusek et al., 2008), lowered elevated cortisol levels following a stressor (Walton et al., 2004) and reduced ATCH levels (Vedamurthachar et al., 2006). Other studies however have found that cortisol levels were unchanged after a 6 week (Pace et al., 2009) and 24-day meditation intervention (Nunes et al., 2007). Together, meditation may only be effective in inducing biological changes following a stressor or when used for an extended period (Ospina et al., 2007).

Voice

The vocal characteristics used in relaxation interventions may play a part in inducing the relaxation response. Research suggests that vocal characteristics, such as voice pitch, tone, volume, and rate of speech, are all moderating factors in the therapeutic process in relaxation techniques that use therapist voice (such as PMR, GI and deep breathing; Bady, 1985). One critical study found that PMR delivered with a decreased tone, volume, and pace (compared to conversation voice, self-relaxation and no treatment control groups) resulted in significant reductions in HR, self-reported anxiety and tension, and improved treatment credibility ratings. Authors suggest that when patients perceive their therapist's voice as relaxing and helpful, they are more likely to commit to taking home relaxation sessions, resulting in better outcomes (Knowlton et al., 2006).

It is unclear whether similar vocal characteristics are important in the virtual human delivered relaxation exercises. Existing literature suggests that people still felt close to a virtual human because of her tone of voice (warm, friendly, and calming; Loveys et al., 2022). However, there were instances where people felt less close because of the lip-syncing problems where the voice was out of time with the movement of the lips. Voice is a factor to consider for relaxation delivered by a virtual human as the lip-syncing may frustrate rather than induce the relaxation response. Including qualitative questions about what participants like and dislike about the virtual human could identify potential improvements to the technology and whether these features are related to healing or physiological outcomes

Music

Music often accompanies relaxation techniques and interventions, and research suggests that this addition is beneficial for physiological arousal states; however, this can be dependent on the type of music and choice. Relaxing music can include smoothing and slow music (played by instruments, e.g., piano, harp, or orchestra) and naturalistic music (i.e., sounds of nature). Studies have found that relaxation interventions accompanied with music have reduced HR in coronary and cancer patients (Tan et al., 2015), reduced pain after gynaecologic surgery (Good et al., 2002), faster EDA recovery (but not HRV; Alvarsson et al., 2010), lower skin temperature (Burns et al., 1999), along with greater self-reported relaxation levels (Burns et al., 1999; Robb, 2000) and reduced self-reported state anxiety (Hammer, 1996; Robb, 2000). Together, this indicates that including relaxing music or giving people a choice of accompanying music can be an effective addition to relaxation interventions to help induce parasympathetic activity.

Review of Evidence in Wound Healing

As demonstrated, there is a plethora of evidence supporting a range of relaxation techniques for use in healthy and patient samples to reduce stress and induce the relaxation response. In a wound-healing context, there is limited but promising evidence that relaxation interventions can effectively improve healing and reduce stress (Robinson et al., 2017). The following section reviews the current literature surrounding relaxation interventions being translated into clinical and experimental wound healing samples. The studies are described in more detail in Table 1 and the results are described in Table 2. While stress reduction is theorised as the main mechanism through which relaxation can improve healing, there is insufficient and mixed evidence behind this theory. Additionally, the differing length and relaxation delivery can make it difficult to discern the most effective way to improve healing and reduce stress.

Table 1.
Summary of wound healing and relaxation studies

Authors (year)	***Participants***	***Intervention***	***Delivery method***	***Wound type***	***Wound healing outcome and time points***	***Results***
Experimentally created wounds						
Gouin et al. (2008)	N = 98 (58 females)	Allocated to one of: 1) 45 min relaxation session (deep breathing, PMR, imagery and self-hypnosis), 2) no relaxation, only quiet reading		Blister would (from a suction blister device)	Day to heal based on 90% return to TEWL baseline criterion	No significant differences in healing between the intervention and control group (p = .053)
Robinson et al. (2015)	N = 121 (87 females)	Allocated to either 1) 20-min relaxation session (deep breathing and PMR) before tape stripping, 2) 20 min relaxation after tape stripping, 3) no relaxation, only quiet reading	Audiotape	Tape stripping on the inner forearm	SBR (measured by TEWL), 25 minutes after tape-stripping	Significantly faster healing in the intervention group than the control (p = .032)
Clinical wounds						
Broadbent et al. (2012)	N = 60 (45 females)	Allocated to either 1) 45-minute and 20-minute relaxation session (deep breathing, PMR, GI) before and after surgery, 2) usual care	Face to face and audiotape	Elective laparoscopic cholecystectomy	Collagen deposition as measured by hydroxyproline, at baseline (before surgery) and 1 week after surgery	Significantly more collagen deposition (faster healing) in the intervention group than the control
Han (2002)	N = 47 (20 females)	Over 4 months participants were allocated to either: 1) a 15minute PMR tape 2) an integrated stress management programme (seven 1-hour sessions in 4 weeks – biofeedback, PMR and	Audiotape	Peptic stomach ulcer	Ulcer healing (rated using gastroendoscopy) from 1 to 6 (with higher scores indicating better healing), at baseline and 4 months	Significantly faster healing in integrated stress management programme than PMR group (p = .05)

Authors (year)	***Participants***	***Intervention***	***Delivery method***	***Wound type***	***Wound healing outcome and time points***	***Results***
		cognitive, emotional coping strategies)				
Holden-lund (1988)	N = 24 (22 females)	One day before and three days after surgery were allocated to either: 1) a 20-minute session (deep breathing, PMR, and GI), 2) 20-minute quiet period	Audiotape	Elective cholecystectomy	Nurse ratings of WAI, at day 3	Significantly lower ratings of erythema (faster healing) in intervention group than control (p <.010)

Table 2.
Physiological measures of stress, stress biomarkers and self-report psychological measures for each study

Authors (year)	***Physiological stress measure, time points measured***	***Results***	***Stress biomarker measures, time points measured***	***Results***	***Self-reported psychological measures, time points measured***	***Results***
Experimentally created wounds						
Gouin et al. (2008)	-	-	Salivary cortisol (ug/dL), 30 minutes before and once an hour for 15 hours after blistering	Lower cortisol production during wounding associated with greater likelihood of being healed on day 4 (p = .016)	Beck anxiety index, 15 minutes before blistering	No significant association between number of days to heal and anxiety
Robinson et al. (2015)	-	-	-	-	Perceived stress scale (PSS-10), 30 minutes before wounding.	No significant association between stress and SBR
					Relaxation and pain levels, at baseline, before tape-stripping, after tape-stripping and at follow up	Significantly higher relaxation levels in the before and after tape stripping groups. A main (but no interaction) effect of time on pain levels

Authors (year)	***Physiological stress measure, time points measured***	***Results***	***Stress biomarker measures, time points measured***	***Results***	***Self-reported psychological measures, time points measured***	***Results***
Clinical wounds						
Broadbent et al. (2012)	-	-	-	-	PSS-4, 3 days before and 7 days after surgery	Significant reductions in stress in intervention group compared to control group – controlling for baseline stress ($p = .048$)
Han (2002)	Galvanic skin temperature, muscle tension level, heart rate, respiratory rate, and skin conductance, before and after intervention	Intervention group had significantly lower muscle tension ($p < .001$), heart rate ($p = .06$), respiratory rate ($p < .001$), and skin conductance ($p = .05$) following the intervention	-	-	Symptoms of stress, before and after intervention	Significant reductions in stress in intervention group from baseline to follow up ($p < .001$)

Authors (year)	***Physiological stress measure, time points measured***	***Results***	***Stress biomarker measures, time points measured***	***Results***	***Self-reported psychological measures, time points measured***	***Results***
Holden-lund (1988)	-	-	Urinary cortisol (lg/ 100 mL per creatinine), 2 days before surgery and every day for 3 days following surgery	Significant reductions in cortisol in intervention group one day after surgery	State anxiety inventory (STAI), 2 days before surgery and every day for 3 days following surgery	Significant reductions in anxiety levels in the intervention group over 3 days after surgery ($p = .01$)

Clinical Wounds

Two early wound healing and relaxation studies had encouraging findings but did not measure psychological stress levels and used subjective healing measures. The first study tested a 20-minute relaxation session (as described in Table 1) before and after surgery with elective cholecystectomy patients and found that those in the intervention group had lower ratings on the wound assessment inventory (consisting of ratings of three major inflammation signs), lower urinary cortisol levels the following day and lower anxiety scores over the three days following the surgery, compared to the control group (See Table 2 for more details; Holden-lund, 1988). The second study tested a longer three-month relaxation intervention and found faster healing in the intervention group than standard care, with an effect size of d=.87 (Rice et al., 2001). These studies support the use of both brief and extended relaxation interventions in patients with surgical and non-healing wounds. However, neither study included a measure of self-reported psychological stress or relaxation, leaving it unclear whether the relaxation exercises were beneficial for these psychological states or associated with healing, as the stress reduction theory suggests. Lastly, the healing measures in these two studies were subjective (e.g., nurse ratings of whether wound is healed or not), limiting these measures' comparability across wound healing studies. Including both or using objective healing measures allows for standardised and clinically relevant measurements.

Another extended relaxation study compared PMR with a more comprehensive integrated stress management program (ISMP; see Table 1 for included techniques) in patients with peptic stomach ulcers. Following the 4-month ISMP intervention, participants had significantly faster healing, lower perceived stress levels, muscle tension, respiratory rate, EDA, and an almost significantly lower HR than those allocated to PMR tapes alone (Han, 2002). While the ISMP group improved healing, reduced sympathetic activity, and improved psychological stress levels, a mediation analysis was not conducted, leaving it unclear whether stress reduction played a role in this relationship. The collection of both physiological and psychological measures of stress adds novel findings to the wound healing literature, but the lack of a control group limits the study. As the ISMP was compared to another active relaxation technique (PMR), it is not easy to discern the true effects of the ISMP and PMR without other confounding effects.

The final relaxation study conducted with clinical wounds was with another elective laparoscopic cholecystectomy patient sample but instead used a longer 45- minute intervention (see Table 1 for details) before and after surgery (Broadbent et al., 2012). This study found that those in the intervention group had more significant hydroxyproline deposition in the wound site at the seven-day follow-up and lowered perceived stress levels than the control (usual care). These findings add to the accumulated evidence that PMR, deep breathing and GI appear effective in improving clinical wound healing and reducing perceived stress levels. However, perceived stress levels did not mediate the relationship between the relaxation intervention and healing outcomes

Acute Experimental Wounds

Relaxation has also been investigated in acute experimental wounds, with mixed findings. In suction blister wounds, a 45-minute relaxation session consisting of deep breathing, progressive muscle relaxation, imagery, and self-hypnosis, was given to participants as the wounding started and a session at one, four and eight hours after the wounding. There were no significant differences in TEWL between the intervention and the control group (quiet reading). However, those with lower cortisol levels were more likely to be healed on day four, suggesting a possible link with HPA activity (Gouin et al, 2008). Authors attribute the null findings to the sample not being sufficiently stressed at baseline, meaning there was no room for meaningful improvements in healing or stress levels following the relaxation session.

Another RCT study by Robinson and colleagues (2015) investigated the effects of the timing of a brief relaxation intervention before or after tape-stripping wounds on SBR compared to a control group. The intervention was a brief 20-minute audiotape that included instructions on deep breathing and PMR exercises and was delivered to a sample of healthy adults through headphones. Soothing background music was added with dimmed lights to facilitate a relaxing atmosphere. There were three groups; the control group read magazines for 20 minutes before and after wounding; the pre-wounding group did relaxation before wounding and read magazines after wounding, and the post-wounding group read magazines prior to performing relaxation after wounding. Compared to the control group, the two groups who performed relaxation before or after the tape-stripping procedure had significantly improved SBR and greater relaxation levels. Pain significantly decreased from baseline to post-recovery in all three groups. Including these psychological variables across time is a strength of study that demonstrates the ability of relaxation to improve psychological outcomes.

However, psychological stress was not measured across the experimental session and perceived stress levels were not significantly associated with SBR. In addition, the lack of association between stress and healing found in Broadbent and colleagues (2012) question the stress reduction mechanism, highlighting the need to investigate this theory further. For example, including a mixture of physiological, psychological and biomarkers of stress collected across multiple time points can objectively measure whether a relaxation intervention has reduced stress (and induced the relaxation response) and whether changes are associated with healing.

The RCT conducted as part of this thesis used the same relaxation script as Robinson and colleagues (2015). However, the current study focused only on delivering the relaxation intervention after wounding and did not investigate timing. The study focused on examining whether a virtual human video recording had a comparable effect on wound healing as an audiotape, compared to a control group that read magazines. As well as examining effects on healing, relaxation, self-reported stress, anxiety, and pain, we also examined physiological effects on HR, EDA, sCort, and sAA as potential stress reduction pathways.

Summary

It is theorised that relaxation works through stress reduction pathways (i.e., HPA and SAM axes) to counterbalance the stress response. There is promising evidence that relaxation interventions can reduce self-reported stress, sympathetic activity, cortisol, and wound healing. PMR, deep breathing, guided imagery and meditation offer robust evidence for improvements in physiological and psychological stress and promising effects on wound healing outcomes, whether used alone or in combination with other techniques (Finger & Arnold, 2002; Toussaint et al., 2021; Robinson et al., 2017). Adding relaxing music in the background of relaxation interventions has also shown to be beneficial for physiological and psychological outcomes, and the voice used should be taken into consideration in the effectiveness of a relaxation intervention.

To date, no research has investigated whether relaxation instructions are effective when delivered by virtual humans compared to simple audio recordings. The study builds upon Robinson and colleagues' (2015) study by comparing the effects of a virtual humans to an audio recording and a control group on SBR, self-reported stress, stress hormones, physiological stress measures using a tape stripping paradigm. Chapter IV will present the rationale for the current study and set out the aims and hypotheses.

Chapter IV: Proposed Study and Hypotheses

Rationale

The introduction to this thesis has argued for the importance of research into whether a virtual human can deliver a relaxation intervention to improve wound healing and reduce stress. Patients are already starting to use various eHealth and mHealth platforms, including mobile apps and websites. Technology can offer a delivery approach that is affordable, easily accessible and integrated alongside existing healthcare practice, and can reduce healthcare burden, provide support for the most vulnerable patients and be a safe alternative to an in-person appointment during a pandemic (Bradbury et al., 2014; Fagherazzi et al., 2020; Murray et al., 2016).

Virtual humans are being developed to deliver health interventions, yet little research has examined their effects on clinical populations and health outcomes (Provoost et al., 2017). Virtual humans are an advanced form of artificial agents, with a unique CGI avatar, advanced neural networks, and multimodal emotional engagement, making them capable of complex social and therapeutic interactions with patients. Their use of relational behaviour and empathy enables them to improve rapport and increase engagement compared with simpler apps (Loveys et al., 2020; 2021). There is promising evidence from pilot and feasibility studies that indicates that virtual human interventions can have benefits compared to control conditions (Chattopadhya et al., 2020). However, RCTs are needed to evaluate their ability to improve psychological stress and health outcomes.

To address this gap in the literature, the current study investigated whether a virtual human relaxation intervention could improve the speed of wound healing and reduce stress compared to traditional audiotaped relaxation. Wound healing is a clinically relevant outcome and can reflect the functioning of the immune system. The study used an experimental acute wound model (tape-stripping) with a healthy population to attempt to isolate intervention effects and reduce confounding factors. Tape stripping is a non-invasive method to remove the top epithelial layer of the skin, and SBR is assessed by measuring trans-epidermal water loss as an objective index of healing. A limitation of some relaxation studies is subjective healing measures (e.g., rating scales), which makes it difficult to quantify and compare the effects of relaxation on healing across studies. Including SBR as an objective healing measure helps address this limitation, although its sensitivity to environmental conditions needs to be acknowledged.

Research has shown that psychological stress has a detrimental effect on wound healing and that interventions to reduce stress can improve healing (Walburn et al.,2009; Robinson et al., 2017). The investigation of how interventions improve healing to date has been hampered by limited assessments of stress and its biological correlates. To help address this, this study collected a mixture of stress outcome measures at three time points: baseline, immediately after the wounding, and after relaxation. Measures include 1) self-reported psychological stress (stress, relaxation, anxiety, and pain levels, 2) HR and EDA as indexes for ANS arousal 3) health behaviours as indexes for an indirect stress measures (sleep, BMI, alcohol intake, exercise, smoking, diet), and 4) stress hormones (sCort and sAA) as indexes for the HPA and SAM axis, respectfully.

There is evidence from several trials that relaxation training can improve the healing of both clinical and experimental wounds when delivered face to face or through human voice recordings (Robinson et al., 2017). However, we do not yet know whether relaxation delivered by a virtual human can produce similar effects. Virtual humans are computer models that, although realistic, is not completely humanlike. Their computer-generated voice, appearance and movements may produce discomfort that does not allow a relaxation response to occur.

To date, no research has investigated whether relaxation instructions delivered by virtual humans are as effective as human audio recordings at improving wound healing, reducing stress, or inducing the relaxation response. Given the novelty of this research, it is also valuable to collect measures of satisfaction, engagement, and open-ended feedback about the virtual human to help interpret the results. This research aims to build upon previous studies with Digital Humans (new type of virtual human) by using a fully powered RCT.

The current study builds upon Robinson, and colleagues' study (2015), which investigated whether relaxation could improve SBR—listening to a 20-minute audiotape of progressive muscle relaxation and deep breathing instructions before or after tape-stripping was found to improve SBR compared to reading magazines. The current study will deliver the same relaxation instructions after tape-stripping. However, the way the relaxation instructions are delivered will be manipulated (delivered either by a Digital Human or a human audio recording) and compared to a control group that read magazines. The results will add to knowledge about the effectiveness and acceptability of virtual agents in providing stress-reduction interventions.

Aims

The primary aim of this study was to investigate whether relaxation instructions delivered by a Digital Human had comparable effects to a human audiotape, and superior effects to a control group, on SBR.

The secondary aim was to investigate whether the relaxation instructions delivered by the Digital Human had similar effects on the biological correlates of stress, as well as self-reported stress, anxiety, pain, relaxation, engagement, and satisfaction, compared to the human audio recording, and superior effects to a control group.

The tertiary aim was to investigate whether self-reported stress and biological markers of stress mediated the relationship between relaxation and wound healing.

Hypotheses

Based on a review of existing literature and research, the hypotheses for the current study are as follows:

1. Participants randomised to the Digital Human or audiotape conditions would have improved SBR after a tape-stripping wound compared to the control group

2. There would be no differences in SBR after a tape-stripping wound between the Digital Human and audiotape groups.

3. The Digital Human condition and audiotape groups would have similar improvements in anxiety, stress, pain, and relaxation levels (psychological variables), EDA and HR (physiological variables), sCort and sAA (stress hormones), and similar engagement and satisfaction ratings, superior to the control group.

4. The effects of relaxation on SBR would be mediated by reduced self-reported stress and biological stress markers.

Chapter V: Methods

This chapter reports the methods of the study, including the trial design, participants, ethics, power analysis, randomisation and blinding, procedure, interventions, outcome measures and statistical analyses.

Trial Design

A randomised controlled trial was conducted to evaluate the effects of different relaxation delivery methods on SBR after tape-stripping. There were three conditions: Digital Human, audiotape, and control (reading magazines). Outcomes were assessed at baseline, immediately post-tape stripping and post-recovery.

Participants

A sample of 159 participants was recruited from the University of Auckland and the wider Auckland community through flyers, mailing lists, and social media advertisements. Participants needed to be over 18 and speak, read, and write in fluent English to be included. Potential participants were excluded if they were allergic to adhesive tape, had an inflammatory skin or immunological-related health condition, took medication that affects immune functioning (e.g., prednisone), was pregnant, were over the age of 60, or had hearing difficulties or vision loss. These exclusion criteria were determined based on variables that can interfere with the measurement of SBR, sAA and sCort (Law et al., 2020a, 2020b, Robinson et al., 2015, 2017).

Ethics

Ethics approval was granted by the Auckland Health Research Ethics Committee on the 3rd of March 2021 for three years (AH21981). The trial was prospectively registered with Australia and New Zealand Clinical Trials Registration under ACTRN12621000442808 on the 16th of

April 2021. See Appendix A for further details. All data were collected under standardised conditions at the University of Auckland's Clinical Research Centre in the Faculty of Medical and Health Sciences in Auckland, New Zealand. At the end of the data collection period, saliva samples were sent to the University of Vienna, Austria for analysis.

Power Analysis

The sample size was calculated using G*Power (Faul et al., 2007), based on previous research that demonstrated that relaxation delivered before or after tape-stripping improved SBR compared to reading magazines with a moderate effect size of f = .28 (Robinson et al., 2017). A power level of .80 and a two-tailed significance level of α =.05 were chosen (Cohen, 1988), for an ANOVA with an expected effect size of f = .28. These parameters gave a required sample size of 132. Following previous tape-stripping studies, this number was increased by 20% to account for possible errors in the TEWL measurements (Law et al., 2020a, 2020b; Robinson et al., 2015; Robles et al., 2007). A final sample size of 159 (53 participants per group) was recruited to give the study adequate power.

Randomisation and Blinding

Participants were randomly assigned to one of three conditions (Digital Human, audiotape, or control) in a 1:1:1 allocation ratio. The allocation sequence was generated using a random online number generator by a person not involved in running the experimental study. The randomisations were placed in sequentially numbered, sealed, opaque envelopes and were kept double-blinded until it was time to set up the relaxation session.

Procedure

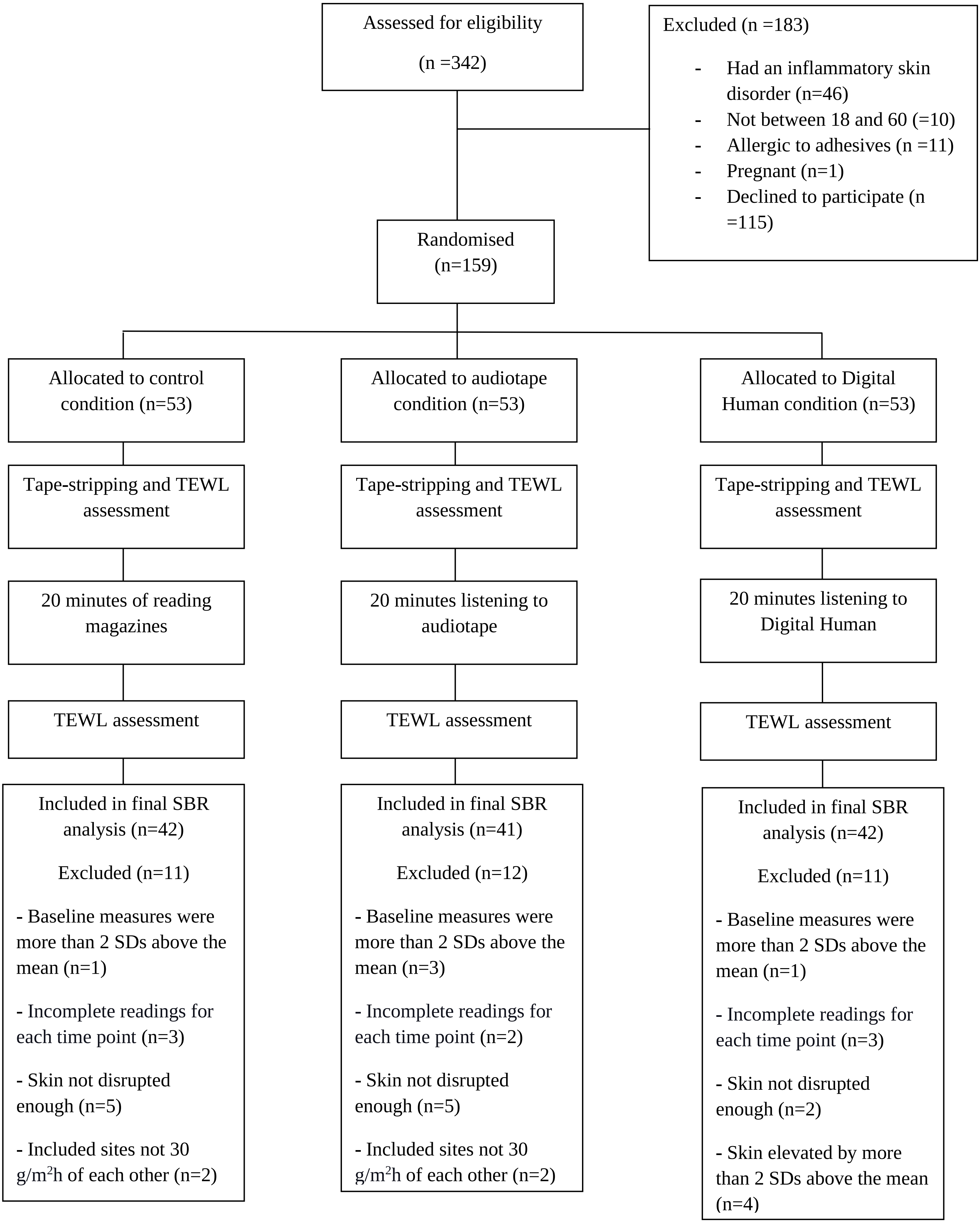
Participants who responded to the study advertisements were provided with the participant information sheet and an opportunity to talk with whānau or support people before participating. If still interested, participants were sent a link to the online eligibility screening questionnaire and were emailed regarding their eligibility with eligible participants further contacted to organise an appointment time.

Following salivary collection guidelines, participants were asked not to chew gum or drink caffeine, juice, and alcohol 18 hours before the session and not eat or brush their teeth the hour before. Participants were also asked not to apply moisturiser on their arms, exercise, or shower within the hour prior to their session to reduce interference in the TEWL measures. The timing of the experimental sessions was limited to between 12:00 pm and 5:30 pm to reduce the effects of sCort and sAA diurnal rhythms (Fries et al., 2009; Strahler et al., 2017). The 90-minute sessions were conducted in a ventilated room with a dehumidifier, per Tewameter probe recommendations to control humidity levels (Robinson et al., 2015).

The experimental procedure is shown in Figure 5. After re-reading the participant information sheet and giving written informed consent, participants completed the baseline measures. Firstly, the Empatica biosensor watch was placed skin-tight to their dominant wrist and kept there for the entirety of the experimental session. Participants filled out the online baseline questionnaire (demographics, health behaviours and psychological variables) on a laptop, provided their first saliva sample and completed the baseline TEWL measures.

Figure 5.

CONSORT diagram illustrating participants' progression through the study procedure and TEWL measurements



After collecting baseline measures, the researcher conducted the standardised tape stripping procedure to disrupt the skin barrier. Immediately after tape-stripping, TEWL readings were measured, and participants completed the second questionnaire (psychological variables) and saliva sample.

Once post tape stripping measures were collected, the randomisation envelopes were opened, and the researcher set up the relaxation session for the 20-minute recovery period. Participants in the audiotape and Digital Human group were told they would be listening to 20 minutes of deep breathing and progressive muscle relaxation exercises through headphones on the laptop. The researcher dimmed the lights to the lowest setting and left the room. Participants in the control group were told to read the selection of magazines while their skin recovered. The lights were not dimmed, and the researcher left the room. Participants were video recorded during the recovery period to measure whether they followed the relaxation instructions and did not touch their tape-stripping wound.

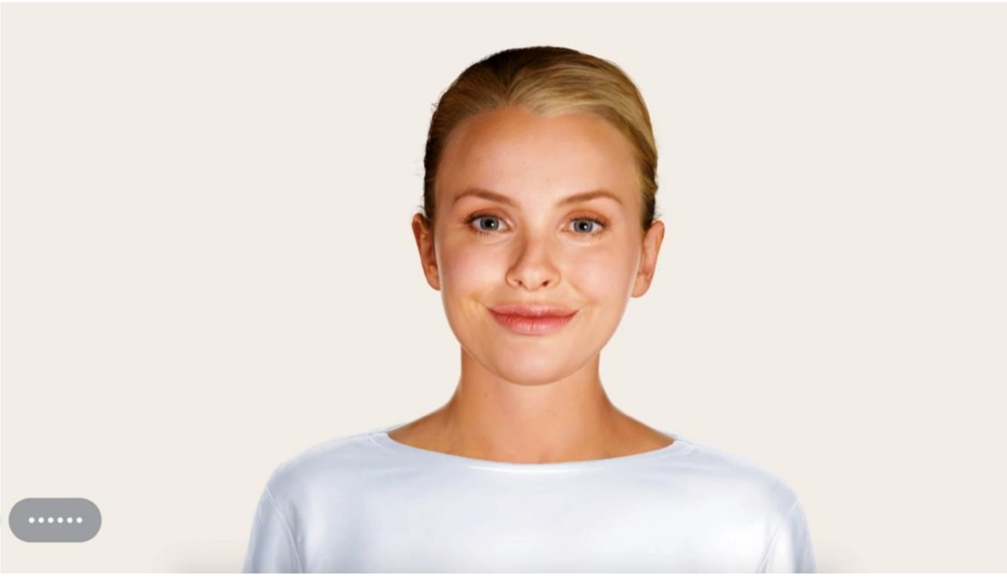
After the recovery period, the researcher returned to the room, and participants completed the post-recovery questionnaire (psychological variables, acceptability, engagement measures, and delivery feedback), provided the final saliva sample, and final TEWL measures were taken. At the end of the session, participants were given a $30 voucher as compensation for their time.

Interventions

Digital Human Condition

Participants assigned to the Digital Human condition were instructed to watch a 20-minute video of “Sam”, the Digital Human, delivering the relaxation exercises. A Digital Human is a new type of virtual human that are being developed by Soul Machines Ltd (Auckland, New Zealand). The virtual embodiments of a Digital Human are synthesised from features of many people and are created with computer-generated imagery (CGI) and lightroom technology (Soul Machines, 2020), distinguishing them from other forms of virtual humans. The Digital Human brain uses a human brain model to create its neuroanatomy and neurotransmitters that control behaviour (Sagar et al., 2016). Through live neural networks, Digital Humans can manipulate their emotional state, speech, facial behaviours, and body gestures, depending on the user's multimodal input. Sam, the Digital Human used in this study was modelled to be a young adult female, with her visual features synthesised from multiple real human models Sam was presented on a white background in portrait view, so her shoulders and head were centred on the screen (see Figure 6).

Figure 6.
The Digital Human interface ("Sam")



Sam was programmed to maintain eye contact and display human-like and naturalistic body gestures (e.g., swaying her shoulders and nodding her head). Her body movements were accompanied by emotional facial expressions, programmed through text-to-speech Emotional Markup Language (EML; Sagar et al., 2014; Sagar et al., 2016**)**. This technique allowed her to express specific facial expressions if she said certain phrases; for example, she elicited a smile, warm eyes, and eyebrows if she said an affirmative word (e.g., yes, or yeah).

Sam used a conversation engine (IBM Watson Agent) that followed a relaxation script comprised of deep breathing and progressive muscle relaxation exercises. Sam spoke with a custom text-to-speech voice package based on a real human voice (same as one used in the audiotape condition). To evaluate the ability of the Digital Human in improve healing, The final intervention was a video recording of Sam reading through the relaxation script with piano background music.

Audiotape Condition

Participants assigned to the audiotape condition listened to a 20-minute audio recording of a real human reading the relaxation script, paired with the same piano background music as the Digital Human condition. The script consisted of deep abdomen breathing exercises and progressive muscle relaxation. Participants were instructed to tense and relax each muscle group (hands, arm, face, neck, chest, back, abdomen, legs, and feet), one at a time.

Control Condition

Participants allocated to the control condition were given four magazines to read through for 20 minutes. Magazines have been used as a control condition in previous studies as a neutral activity to prevent participants from experiencing negative emotions or stress from becoming too bored (Robinson et al., 2017).

Measures

Baseline Measures

The following measures were used to describe the sample and control for any differences between groups as these variables have been previously shown to affect healing and immune parameters (Law et al., 2020a, 2020b; Maarouf et al., 2019; Robinson et al., 2017).

Demographics

Participants were given a demographics questionnaire at baseline that included age, weight, height, ethnicity, employment status and education level, used in previous wound healing studies (Koschwanez et al., 2017; Law et al., 2020a; Robinson et al., 2015). Collecting data on these variables allowed for a description of the sample, subgroup analyses, and comparisons of the groups at baseline.

Health Behaviours

Health behaviours were assessed at baseline because they have been associated with stress, immune outcomes, and tape-stripping (Maarouf et al., 2019; Robinson et al., 2017). The baseline questionnaire included questions about alcohol consumption, physical exercise, diet, smoking status, and sleep, as measured in previous tape-stripping studies (Law et al., 2020a, 2020b; Robinson et al., 2015).

Alcohol consumption was assessed from 1 (never) to 6 (every day) in the past three months. Participants were asked how often they did more than 30 minutes of physical exercise in an average week, from 1 (never) to 8 (every day). Diet was self-assessed from 1 (very poor) to 5 (very good) in the past week. Participants were also asked to provide their smoking status and the number of hours they slept in the past 24 hours.

Perceived Stress

The 10-item Perceived Stress Scale (PSS) was administered at baseline to assess how stressful, unpredictable, and uncontrollable participants perceived their lives (Cohen, 1983). For each question, participants rated how often they felt or thought a certain way in the last month on a scale from 0 (never) to 4 (very often). Scores were totalled across items to give a final score between 0 and 40. Higher scores on the PSS indicate that participants were experiencing a greater level of perceived general life stress than those with lower PSS scores. The scale has shown good reliability (α >.70) and validity in different ethnicities and clinical samples (Broadbent et al., 2012; Koschwanez et al., 2017; Lee, 2012).

Primary Outcome Measures

Tape Stripping and SBR

Tape-stripping is an experimental and standardised wounding technique that removes the outer layer of skin (the stratum corneum) through repeated application and removal of adhesive tape (Altemus et al., 2001). The skin barrier is disrupted and loses its ability to regulate water movement in and out (Walburn et al., 2009). Tape stripping was therefore used in the current study to model wound healing in a non-invasive, minimally painful, and quick manner. The following section details the tape-stripping procedure used in the current study, akin to previous research (Law et al., 2020a, 2020b; Robinson et al., 2015).

A baseline measure of skin barrier function was determined by collecting TEWL measures from a Tewameter TM300 probe (Courage + Khazaka, Germany) which measured the evaporation rate (g/m^2h) in the air layer next to the skin (Law et al., 2020b). The Tewameter probe was preheated to 35°C (skin temperature; Koschwanez & Broadbent, 2011). TEWL is a measure of the skin's ability to prevent water loss. A high TEWL measurement indicates poor skin barrier function and an increase in water evaporating through the skin. When the skin barrier is disrupted by the tape stripping procedure, TEWL increases as the skin loses its ability to control water loss. As the skin barrier heals, TEWL returns to baseline levels, and this change in TEWL over time provides a measure of SBR and an estimate of wound healing.

The tape-stripping procedure was conducted on the participant’s non-dominant forearm. Participants placed their forearm flat on a pillow, and four $1cm^2$ sites were marked on the inside of their forearm, 1cm below the elbow crease. The bottom site was left undamaged as the control site. The Tewaemeter probe was gently placed against the skin on each of the four sites (one at a time) for 60 seconds, taking one measurement every second.

Once the baseline TEWL measures were taken, the three test sites were dry shaven to ensure that hair was not pulled during the tape-stripping procedure. Standardised packaging tape (Scotch Commercial Grade Packaging Tape, 3M) was used for the tape-stripping procedure. New pieces of tape were applied with pressure to the three test sites and gently peeled off. After the first 20 strips of tape, TEWL was measured to determine whether it had reached 15 g/m^2h above baseline. If not, ten more strips were applied, and TEWL was measured again. The tape was applied until TEWL was elevated to 15 g/m^2h above baseline or until 40 pieces of tape were used. A TEWL measurement for each site was then collected to determine skin barrier impairment levels immediately following the tape-stripping procedure.

Participants were instructed not to touch or cover their wound for the rest of the session to minimise interference with the healing process. The final measure of TEWL was taken after the 20-minute recovery period once all other measures were completed.

TEWL Analysis

An overall TEWL reading for each site and time point was determined by averaging 20 consecutive measurements with a standard deviation below 0.6. The following formula was used to get the final SBR percentage from the TEWL readings: $(TEWL_{elevated} – TEWL_{recovery}) / (TEWL_{elevated} – TEWL_{baseline}) \times 100$ (Robles, 2007; 2009). A higher percentage means a higher SBR during the recovery period, indicating faster wound healing. There was a large variation in the TEWL data across the sample, possibly as the room temperature was not controlled. TEWL data were screened and only included if valid.

As shown in Figure 5, SBR values were excluded if baseline TEWL readings were more than 2 standard deviations (SDs) above the mean (n=5), readings were not complete for each time point (n=7), skin was not elevated enough (more than 5g/m^{2}h above baseline; n=12) or skin was damaged more than two SDs of elevation above the mean (n=4), as these denoted outliers in the data.

After initial exclusion, the SBR values of the remaining sites were all averaged if they were all within 10g/m^{2}h of each other. If not, the two closest two sites were averaged if they were within 30g/m^{2}h, as this indicated they were unreliable readings (n=4). After exclusion, there were 42 participants in the control condition, 41 participants in the audiotape condition and 42 participants in the Digital Human condition. TEWL has concurrent validity with gravimetrically assessed absolute water loss rates (Fluhr et al., 2006).

Secondary Outcome Measures

Psychological Measures

Participants were given four visual analogue scales (VASs) at each time point to measure their self-reported levels of relaxation, stress, anxiety, and pain. To do this, participants dragged a slider to mark an exact number between 0 and 100 to indicate how they were currently feeling at the time.

The relaxation scale ranged from "not relaxed at all" to "extremely relaxed", the stress scale from "not at all stressed" to "extremely stressed", the anxiety scale from "not at all anxious" to very anxious" and the pain scale from "no sensation of pain" to "most sensation of pain imaginable". A higher score indicates that the participant has greater relaxation, stress, anxiety, and pain levels at each time point. These measures have been used in previous tape stripping and psychological intervention studies to assess acute psychological states across the experimental session (Law et al., 2020a; 2020b; Robinson et al., 2015). Measurement errors or missing data (i.e., from participants accidentally not dragging the slider) were coded as missing data in the final psychological variable analysis.

Physiological Measures

Participants were given a wearable biosensor (Empatica E4) watch on their dominant wrist to collect biometric data. The watch collected continuous data for the entirety of the session and was time-stamped after each questionnaire was completed. HR and EDA (i.e., electrodermal activity) were collected as two physiological stress response measures that reflect the degree of parasympathetic or sympathetic arousal (Ahmed et al., 2015; Amin & Faghih, 2018; Betti et al., 2017)**.** Electrodermal activity was processed using a validated tool which removed confounding artefacts in the data (Taylor et al., 2015). The measure of HR was derived from the blood volume pressure rates. The final HR and EDA value for each time point (baseline, post-tape-stripping and post-recovery) were averaged from the minute before and after the time-stamped marker.

Salivary Stress Biomarkers

Saliva samples were taken at the three-time points using standardised SaliCaps collection devices (IBL, Hamburg, Germany). These samples were collected to measure sCort and sAA to determine differences across conditions and whether changes over time mediated the relationship between condition and SBR.

Participants first were offered a glass of water to rinse their mouths and swallow. For the next two minutes, they were instructed to collect saliva in their mouth naturally (without swallowing), using the passive drool technique, before transferring their saliva into a SaliCap (a saliva storage tube). After collection, the saliva samples were stored at -20°C at the University of Auckland. Due to COVID-19 lockdown and associated recruitment delays, the samples are currently being shipped for analysis on dry ice to the University of Vienna, Austria, and were not included in the results section of this thesis. sAA concentrations will be determined using a commercial enzyme-linked immunosorbent assay (ELISA, IBL, Hamburg, Germany), while sAA was determined by a kinetic colormetric test with reagents from Roche (Roche Diagnostics, Mannheim, Germany; Law et al., 2020a; Robinson et al., 2017).

Engagement and Satisfaction

In the post-recovery questionnaire, participants completed two VASs (from 0 to 100) to rate how satisfied and engaged they found the relaxation session. The engagement question was labelled from "not engaging at all" to extremely engaging", and the satisfaction one was "not at all satisfied" to "very satisfied".

Relaxation Session Feedback

The final two questions in the post-recovery questionnaire were open-ended to gauge opinions about the relaxation session. The first question asked, “What did you like about the delivery of the relaxation session?” and the second, "How do you think the delivery of the relaxation session could be improved?”. These questions were adapted from Loveys and colleagues' feasibility study (2022) investigating Digital Humans and CBSM.

Observational Coding of the Recovery Period

The extent to which participants followed the relaxation instructions and did not touch their wound were coded from the video recordings of the 20-minute recovery period. This was to control for potential influences in the healing process, as collected in previous tape-stripping studies (Law et al., 2020a; 2020b). The instructions variable was coded 1 if participants appeared to follow the instructions (e.g., using the headphones, closing their eyes, or reading the magazines) and 0 if participants were not following instructions (e.g., if they started using their phone or stopped listening through the headphones). The touch variable was coded 1 if participants touched or covered their tape-stripping wound and 0 if the participants did not touch or cover their wound. Each video was split into 5-minute blocks, and if at least one block was coded with a 1, the participant was coded as an overall 1 (indicating that they did not follow the relaxation instructions or touched their wound). The data was then converted into a percentage for each group to indicate the proportion of participants who followed the instructions and did not touch their wound (Law et al., 2020a; 2020b).

Statistical Analysis

Data were analysed using IBM SPSS Statistics version 28. The data were checked for errors, outliers, and violations of the normality assumption before analysis. To test the assumption of normality, Shapiro-Wilk tests were performed, with results of p <.001 considered a violation of the normality assumption. Bootstrapping was used for variables that violated the normality assumption. A statistical significance level of p <.05 was maintained for the main analyses.

To assess differences between groups in demographic and baseline variables, Pearson's Chi-Square test of contingencies or one-way ANOVAs was conducted. Variables that violated the assumption of expected cell frequencies were grouped together after a sensitivity analysis or Fisher's Exact tests were conducted.

To evaluate the primary outcome, the effect of relaxation condition on SBR, a 3-step hierarchical regression was conducted while controlling for covariates in the first two steps of the model (Hypothesis 1 and 2). Tape-stripping variables known to effect SBR (number of strips of tape and levels of skin barrier impairment) were added into the first step of the model. Variables that differed at baseline (sleep hours, employment status, and relaxation levels) and known covariates from previous studies were entered into the second step of the model (BMI, age and gender; (Law et al., 2020a; Robinson et al., 2017). As the condition was a categorical variable, it was first dummy coded before being added to the analysis so that audiotape and Digital Human were compared to the control condition.

ANCOVAs were conducted to assess the effects of condition on the psychological and physiological variables (Hypothesis 3). Bootstrapping was used on data that violated assumptions of normality (relaxation and EDA). Self-reported stress, relaxation, pain, anxiety levels, and HR and EDA were converted into change scores, using the difference between the baseline and post-recovery time points. The change scores were analysed with an ANCOVA controlling for baseline levels (this helps to account for any baseline differences between groups due to chance, and control for regression to the mean, as recommended by Vickers and Altman (2001)

To assess condition effects on satisfaction and engagement levels, one-way ANOVAs were conducted (Hypothesis 3).

Responses to the two open-ended questions were assembled into the most frequent topics after a simple thematic analysis was conducted. Informed by the data, an inductive approach was used to create themes. The six final themes were ‘appearance’, ‘voice’, ‘music’, ‘environment’, ‘pace’, and ‘content’. ‘Appearance’ was only present for the Digital Human condition, and ‘voice’ was only present for the audiotape and Digital Human conditions. The other four themes were present in all three conditions. The six themes were further coded into strengths or limitations, giving twelve categories. The total count for each category was converted into a percentage to indicate the proportion of each limitation and strength in the themes. As some participants did not provide an answer to these questions, the total category count and proportions did not add up to the total sample and group sizes.

Mediation analyses were planned to assess whether any of the psychological or physiological variables mediated the relationship between group and healing (Hypothesis 4) but were not conducted due to a non-significant group effect on healing

Chapter VI: Results

This chapter reports the results of the study. First, recruitment, demographic, and baseline characteristics are described. This is followed by analyses of the primary outcome (SBR), the secondary outcomes (psychological and physiological), satisfaction and engagement, open-and ended responses. Finally, a mediational analysis is presented.

Recruitment

Participants were recruited between 26th May 2021 and 22nd February 2022. Due to nationwide lockdown and covid-related restrictions, recruitment was paused from 17th August 2021 to 2nd December 2021.

Baseline Characteristics of the Sample

The sample (n = 159) consisted of 116 females, 41 males, and 2 non-binary/other, with an average age of 26.04 years (*SD*=7.91). A summary of the sample's demographic characteristics and baseline measures is shown in Table 3 for each intervention group. Significant differences were found between groups at baseline in hours of sleep (most sleep in the control group and least sleep in the audiotape group) and relaxation levels (the control group was most relaxed, and the Digital Human group was the least relaxed at baseline). Due to randomization, these differences were due to chance alone

Table 3.
Summary of Demographic Baseline Characteristics across Intervention Groups

Characteristic	*Control*	*Audiotape*	*Digital Human*	*p*	η_p^2
Demographics					
Age (years), M(*SD*)	25.85 (9.65)	25.58 (6.36)	26.69 (7.45)	.758	.004
Range	18 - 57	18 - 47	19 - 58		
Gender, n (%)				.747	.007
Female	41 (77.4%)	38 (71.7%)	38 (71.7%)		
Male	12 (22.6%)	15 (28.3%)	15 (28.3%)		
Ethnicity, n (%)				.361	.07
European	26 (50%)	18 (34%)	27 (51%)		
Māori/ Pacific Peoples	4 (8%)	5 (10%)	2 (4%)		
Asian	22 (42%)	29 (56%)	24 (45%)		
Highest Education, n (%)				.069	.27
Secondary School	24 (45%)	17 (32.7%)	9(17.3%)		
Technical Certificate/ Undergraduate Degree	16 (30%)	18 (34.6%)	22(42.3%)		
Postgraduate Degree	13 (25%)	17(32.7%)	21(40.4%)		
Employment Status, n (%)				.451	.04
Employed full time	9 (17%)	15 (28.3%)	16 (30.2%)		
Employed part time	9 (17 %)	3 (5.7%)	5 (9.4%)		
Student	31 (58.5%)	32 (60.4%)	29 (54.7%)		
Not currently employed	4 (7.5%)	3 (5.6%)	3 (5.7%)		
Health Behaviours					
BMI, M (*SD*)	23.40 (3.81)	23.63 (3.83)	23.97 (4.26)	.758	.004
Exercise (days/week), M (*SD*)	3.42 (2.07)	4.34 (2.26)	3.71 (1.84)	.069	.034
Diet Quality (rating out of 5; 1 = very poor, 5 = very good), M(*SD*)	3.51 (.61)	3.36 (.74)	3.36 (.71)	.428	.072
Sleep (hours/night), M(*SD*)	7.51 (.95)	6.49 (2.09)	7.18 (1.34)	.003	.277
Sleep Quality (rating out of 4; 1 = very bad, 5 = very good), M(*SD*)	2.91 (.564)	2.79 (.661)	2.91 (741)	.595	.007
Alcohol Intake, n (%)				.415	.254
Not at all	10 (18.9%)	13 (24.5%)	13 (24.5%)		
Less than once a month	22 (41.5%)	10 (18.9%)	8 (15.1%)		
1-3 times a month	12 (22.6%)	21 (39.6%)	21 (39.6%)		
1-6 times a week	9 (16.9%)	9 (17%)	11 (20.7%)		

Table 3.
Summary of Demographic Baseline Characteristics across Intervention Groups

Skin permeability barrier					
Baseline TEWL, averaged across sites (g/m²/h), M(*SD*)	19.47 (5.12)	18.72 (5.24)	19.81 (5.37)	.547	.008
Level of skin barrier impairment across disrupted sites (g/m²/h), M (*SD*)	33.44 (11.4)	30.54 (8.73)	34.96 (12.06)	.106	.03
TEWL reading at post-recovery (g/m²/h), M *(SD*)	28.6 (9.31)	26.6 (7.39)	29.97 (10.94)	.218	.020
Number of strips used, M (*SD*)	34.91 (7.75)	36.35 (7.41)	33.05 (8.38)	.287	.016
Psychological Measures					
PSS, M(SD)	18.66 (4.86)	17.17 (3.77)	18.43 (4.28)	.172	.023
Stress	28.66 (21.9)	33.08 (25.5)	40.53 (27.95)	.053	.037
Relaxation	70.88 (24)	63.42 (27.4)	57.09 (29.15)	.033	.043
Anxiety	16.23 (21.9)	24.74 (23.6)	24.84 (27.64)	.119	.027
Pain	8.3 (16.36)	8.58 (13.32)	9.54 (18.53)	.918	.001
Physiological Measures					
HR, M (*SD*)	80.38 (9.33)	80.67 (11.8)	82.03(8.86)	.122	.005
EDA, M (*SD*)	.69 (1.51)	.263 (.42)	.66 (1.29)	.695	.029

Note: M=Mean, *SD* = Standard deviation, % = percentage of participants in that category. P-values were calculated by one-way ANOVAs and Chi-square tests

Observed Coding of the Recovery Period

On average, 86% of participants in the Digital Human group, 92% of participants in the audiotape, and 89.8% of participants in the control group followed the instructions of their allocated intervention group. On average, 96% of participants in the Digital Human group, 93.8% of participants in the audiotape group and 98% of participants in the control group followed the healing instructions and did not touch their wound during the recovery period.

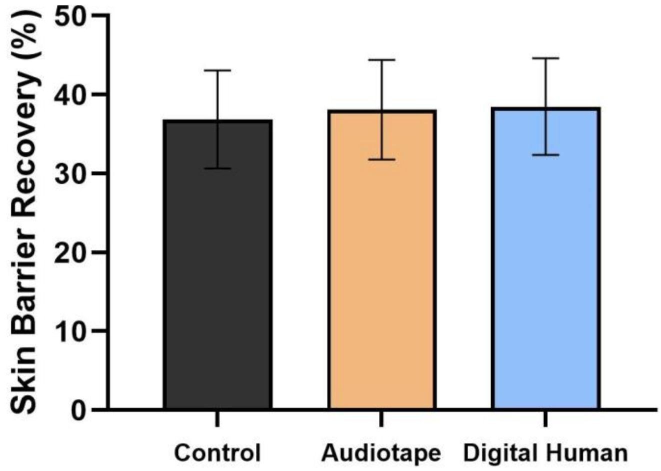
The level of following intervention and healing instructions were not significantly associated with any of the outcomes and so were not controlled for in any further analyses.

Primary Outcome: Effects of Intervention Group on SBR

Mean SBR scores across groups, controlling for covariates, is shown in Figure 7. It was hypothesised that participants randomised to the Digital Human or audiotape group would have improved SBR after a tape-stripping wound compared to a control group. The secondary hypothesis was that there would be no differences in SBR after a tape-stripping wound between the Digital Human and audiotape groups. A three-step hierarchical regression was conducted to analyse the effects of the dummy codes for condition on SBR. The coefficients and *F* change scores for each step of the model are shown in Table 4. In step 1 of the model, the number of strips and level of skin impairment accounted for a significant 53% of the variance in SBR, $R^2 = .053$, $\Delta F\ (2, 120) = 3.325$, $p = .039$. On step 2, sleep hours, baseline relaxation levels, BMI, age, and gender were added to the model and accounted for an additional non-significant 7.8% of the variance in SBR, $\Delta R^2 = .078$, $\Delta F\ (5, 115) = 2.074$, $p = .074$. Adding the dummy codes for condition into Step 3 of the model did not significantly explain any additional variance in the model, $\Delta R^2 = .001$, $\Delta F\ (2, 113) = .156$, $p = .952$, indicating that SBR was not significantly different between the intervention groups (audiotape and Digital Human) and control group.

Figure 7.

Adjusted mean SBR across groups, controlling for covariates.



Note: Error bars represent 95% confidence intervals.

Table 4.
Regression Coefficients for Each Predictor Variable on Each Step of a Regression Model Predicting SBR

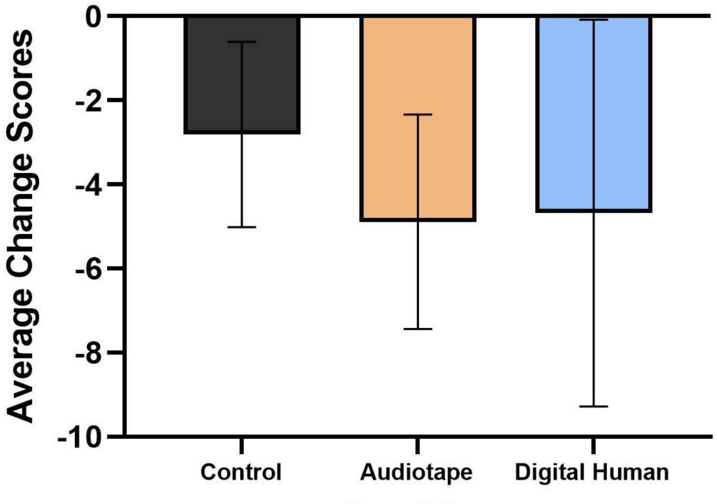
Variable	*B*	*[95% CI]*	*SE B*	*β*	*p*	R^2	*ΔF*
Step 1 (Constant)						.053	3.325
Strips	.18	[-.36, .73]	.28	.07	.512		
Skin Impairment	-.42	[-.89, .05]	.24	-.19	.081		
Step 2 (Constant)						.078	2.074
Strips	.05	[-.49, .59]	.276	.012	.855		
Skin Impairment	-.48	[-.96, -.02]	.238	-.22	.043		
Gender	1.25	[-6.30, 8.81]	3.82	.03	.743		
Age	.04	[.46, .53]	.250	.02	.876		
BMI	.98	[.07, 2.02]	.527	.17	.066		
BL Relaxation	.13	[-.003, 2.6]	.066	.17	.055		
Sleep Hours	-1.59	[-3.86, .69]	1.15	-.12	.169		
Step 3 (Constant)						.001	.156
Strips	.051	[-.50, .60]	.279	.02	.856		
Skin Impairment	-.489	[-.96, -.01]	.240	-.22	.044		
Gender	1.190	[-6.49, 8.87]	3.88	.03	.760		
Age	.029	[-.474, .53]	.254	.01	.909		
BMI	.976	[-.079, 2.03]	.532	.17	.069		
BL Relaxation	.133	[-.003, .27]	.069	.18	.055		
Sleep Hours	-1.55	[-3.94, .83]	1.20	-.12	.200		
Audiotape Condition	.69	[-8.42, 9.81]	4.60	.02	.880		
Digital Human Condition	1.39	[-7.47, 10.27]	4.48	.03	.755		

Note. CI = confidence interval

Secondary Outcomes: The Effects of Intervention Group on Psychological Outcomes

It was hypothesised that the Digital Human and audiotape groups would have similar improvements in anxiety, stress, pain, and relaxation levels. ANCOVAs were conducted to analyse the change scores of each psychological variable from baseline to follow up (controlling for baseline scores). This analyses showed that, after accounting for baseline stress levels, there were no significant differences in stress changes scores ($F_{(2,158)}$=1.599, p=.205, η_p^2= .020). Figure 8 presents average stress change scores for each group.

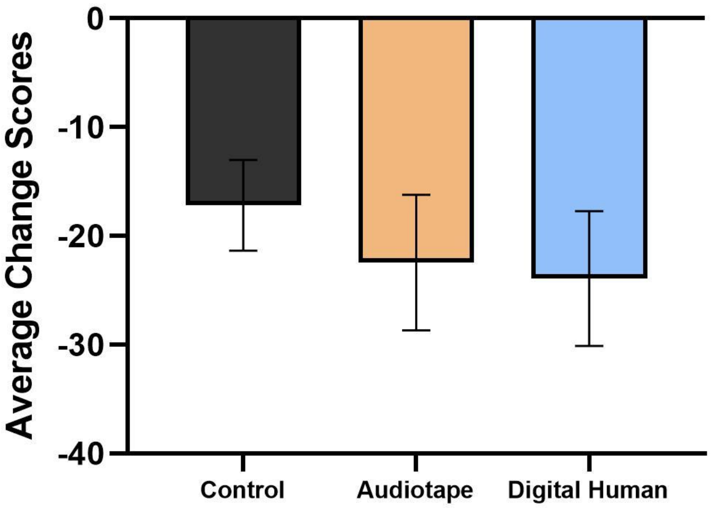
Figure 8.
Bar graph showing average pain change scores by group



Note: Error bars represent 95% confidence intervals.

After accounting for baseline pain levels, there were no significant differences in pain changes scores ($F_{(2,158)}$=.271, p=.763, η_p^2= .006) and Figure 9 presents the average pain change scores for each group.

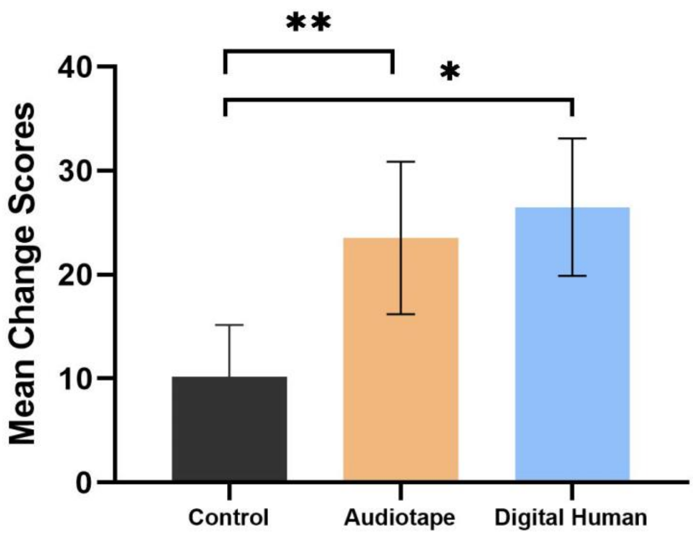
Figure 9.
Bar graph showing average stress change scores by group



Note: Error bars represent 95% confidence intervals.

There was a significant difference in relaxation change scores in relaxation levels between groups ($F_{(2,151)}$=5.432, *p*=.005, η_p^2= .067). Figure 10 presents average relaxation change scores for each group, showing the significant comparisons. Post hoc tests showed that the audiotape (*M*=23.52, *SD*=26.06) group had significantly greater change scores than the control condition (*M*=10.17, *SD*=17.91, *p*=.002, d=.59). The digital condition (*M*=26.48, *SD*=23.69) was significantly more relaxed than the control condition (*p*=.013, d=.78). There were no significant differences between the audiotape and digital condition (*p*=.586, d=.12).

Figure 10.
Bar graph showing average relaxation change scores by group

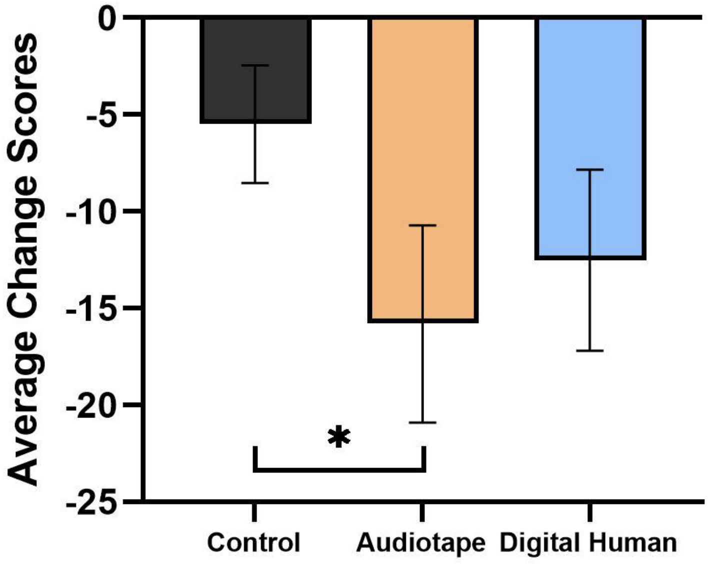


Note. 95% Confidence intervals are depicted. (**p <.01, *p<05).

Changes in anxiety levels were significantly different between groups ($F_{(2,158)}$=5.888, *p*=.016, η_p^2= .052) and Figure 11 presents average anxiety change scores for each group, and the significant comparison. Post hoc tests revealed that the audiotape group had significantly greater reductions in anxiety (*M*=-15.81, *SD*=18.48) compared to the control condition (*M*=-5.49, *SD*=11.03, p=.004, d=.68). There was no significant difference in anxiety change scores between the digital (*M*=-12.53, *SD*=16.96) and control condition (p=.160, d=.49) and no significant differences between the audiotape and Digital Human group (p=.131, d=.19).

Figure 11.

Bar graph showing average anxiety change scores by group



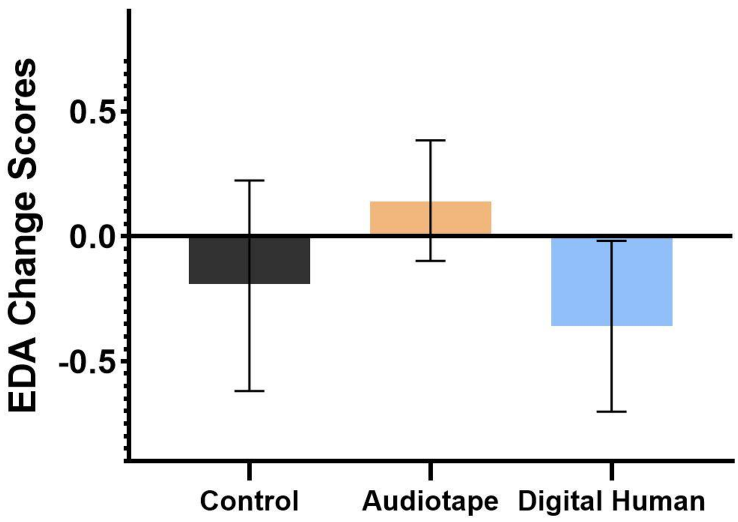
Note. Error bars represent 95% confidence intervals (*p <.05).

Secondary Outcomes: Effects of Intervention Group on Physiological Variables

It was hypothesised that the Digital Human and audiotape groups would have similar improvements in EDA and HR (physiological variables), superior to the control group. Figure 12 presents the mean EDA change scores (between baseline and post-recovery) between groups. There were no significant differences in changes in EDA scores between groups ($F_{(2,142)}$=1.140, p=.323, η_p^2= .016).

Figure 12.

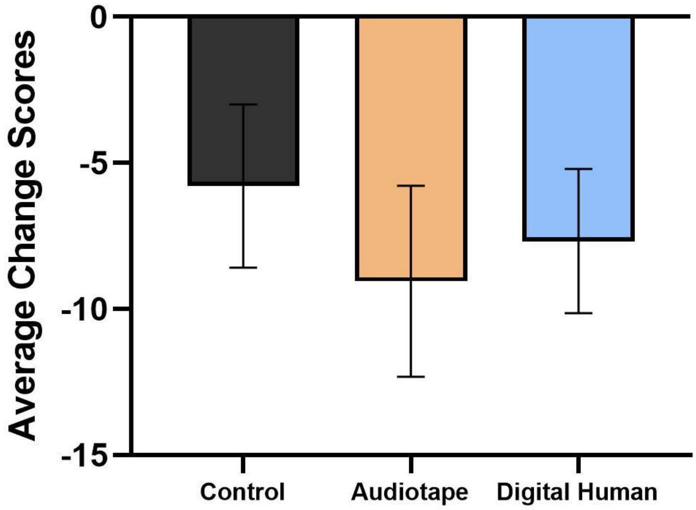
Bar graph showing average EDA change scores by group



Note. 95% confidence intervals are depicted. EDA = Electrodermal Activity

Figure 13 presents the average HR change scores (between baseline and post-recovery) between groups. ANCOVAS revealed no significant differences in changes in HR scores between groups after controlling for baseline scores ($F_{(2,144)}$=1.74, p=.180, η_p^2= .024).

Figure 13.
Bar graph showing average HR change scores by group



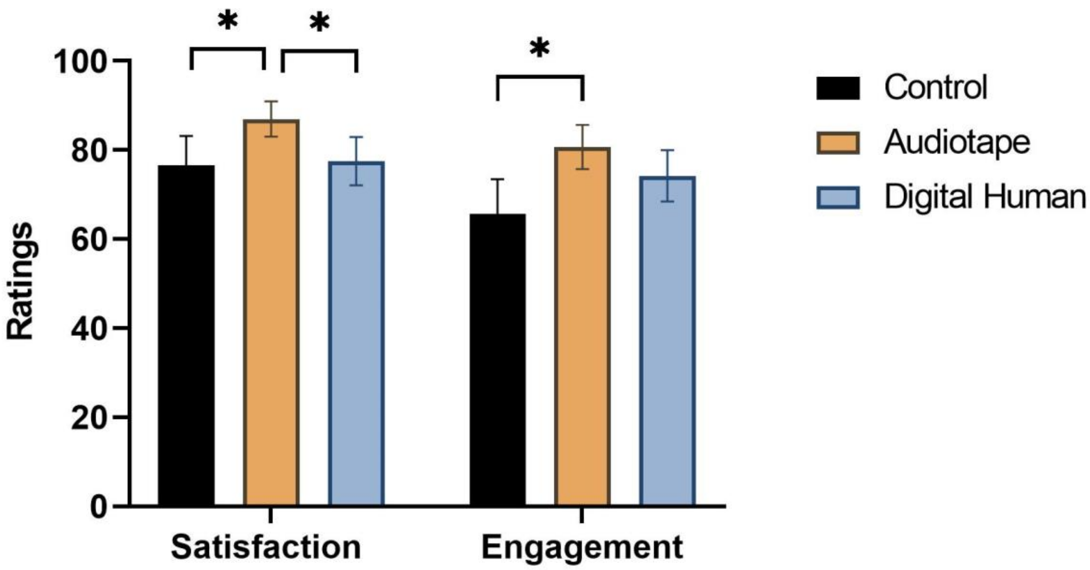
Note. 95% confidence intervals are depicted

Secondary Outcomes: The Effects of Intervention Group on Satisfaction and Engagement

It was hypothesised that the Digital Human and audiotape groups would have similar satisfaction and engagement ratings, superior to the control group. A bar graph showing ratings of satisfaction and engagement by group is displayed in Figure 14. One way ANOVAs found a significant difference in satisfaction scores between groups ($F_{(2,158)}$ =4.54, p=.012, η_p^2=.055). Follow up tests using Tukey's HSD revealed that the audiotape group was significantly more satisfied with their relaxation intervention (M=86.96, SD=14.36) than the Digital Human (M=77.51, SD=19.68, p=.037, d =.55) and control groups (M=76.60, SD=23.65, p=.020, d=.53). There were no significant differences between the Digital Human and control groups (p=.969, d =.04)

There was a significant difference between engagement scores between groups ($F_{(2,157)}$ =5.82, p=.004, η_p^2=.070). Follow up tests using Tukey's HSD showed that the audiotape group was significantly more engaged with their relaxation intervention (M=80.68, SD=18.01) than the control group (M=65.73, SD=27.63, p=.002, d =.64). There were no significant differences between the Digital Human group (M=74.27, SD=20.92) and audiotape group (p=.305, d=.33) or between the Digital Human and control group (p=.133, d=.35)

Figure 14.
Bar graphs showing ratings of satisfaction and engagement ratings by group



Note: Bars represent 95% confidence intervals for group means. * $p < .05$.

Secondary Outcomes: Open-ended Responses

Participants identified several strengths and limitations of each intervention group through the open-ended responses. The results are presented by intervention group with a summary of responses, bubble plots (presented in Figures 15, 16 and 17) and a table of representative quotes (presented in Tables 5, 6, and 7).

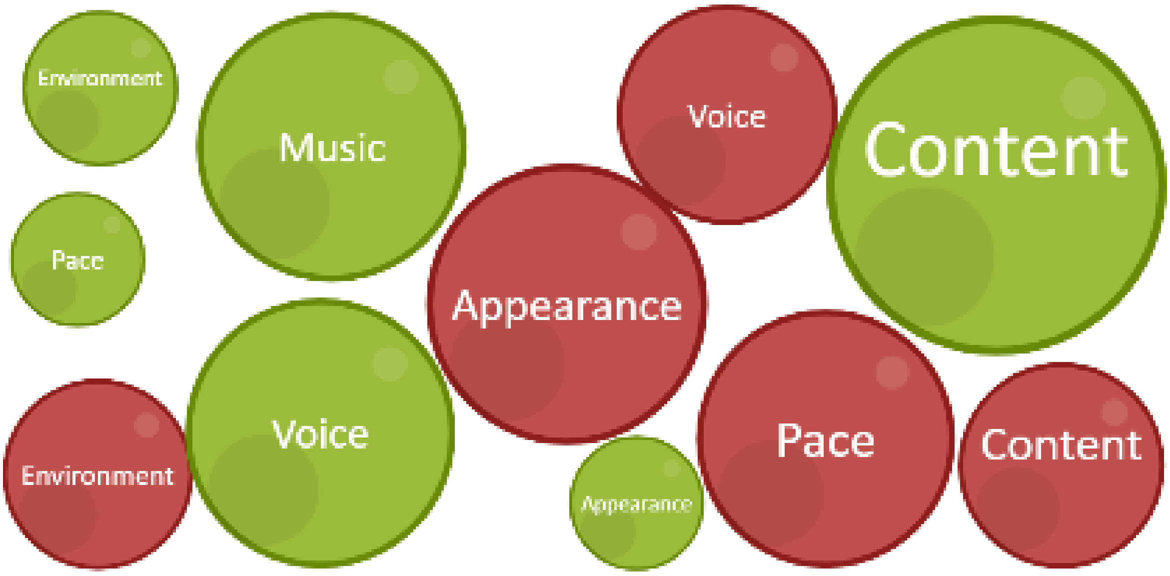
Digital Human Group

Overall, the largest proportion of strengths were related to content (35.9%), voice (22.6%), music (22.6%) and environment (7.5%), as depicted in Figure 15. Participants liked the step-by-step guidance and clear instructions through each deep breathing and muscle group, the calming and soothing tone of Sam's voice, the background music and how it complemented Sam's voice, the use of headphones to isolate the exercises and the darkened room, as illustrated in some of the representative quotes in Table 5. A few participants liked her naturalistic body movements (e.g., swaying) and her calming mannerisms (appearance, 5.7%) and the length of the exercises (pace, 5.7%).

The largest proportion of limitations were related to appearance (24.5%) and pace (20.75%), as depicted in Figure 15. For example, participants felt that Sam's appearance was appeared too robotic, the lip syncing between the voice and lip movements were off, some of the breathing cues did not flow or time right and became too predictable. Voice (15.1%), content (13.2%) and environment (11.3%) were all similar proportions. As illustrated in Table 3, some participants mentioned that the relaxation exercises did not require Sam's visual embodiment as they had their eyes closed for most of the session. Some participants did not request any improvements and no participant disliked the background music or reported that they would have preferred to interact with a real human.

Figure 15.

Bubble plot depicting the proportion of strengths and limitations for each theme in the Digital Human group.



Note: The size of the bubbles represents how common each theme was, and the colours represent green for strengths and red for limitations.

Table 5.
Representative quotes for the strengths and limitations of each theme in the Digital Human group.

Theme	*Strengths or limitations*	*N*	*Representative quote [Participant ID]*
Appearance	Strengths	3	"I liked how the person moved like an actual person it made it feel less awkward" [p85]
	Limitations	13	"The Digital Human's mouth moved just a bit slower than the words so that was a little disconcerting." [p29]
Voice	Strengths	12	"The person had a nice calm voice/manner" [p75]
	Limitations	8	"It felt a bit jolty at the start of her sentences" [p138]
Music	Strengths	12	"The relaxing music in the background really complemented the relaxed tone of voice." [p59]
Pace	Strengths	4	"It was a good duration (20 minutes) and did not have too many blank patches. I liked that the timer was visible." [p105]
	Limitations	11	"The breathing cues were slightly fast and the simulated person was quite repetitive." [p116]

Environment	Strengths	5	"Having the lights dimmed and being alone, also having the headphones to help isolate external noises" [p12]
	Limitations	6	"Allow us to do it lying down" [p43]
Content	Strengths	25	"I loved the deep breathing and the muscle technique for relaxation. The guidance through the relaxation was also nice." [p116]
	Limitations	7	"The refrains that were used were predictable, whether there could be other ways of directing breathing?" [p24]

Audiotape Group

Overall, the largest proportion of strengths were related to content (35%), voice (22%), and music (22%), as depicted in Figure 16. Participants liked the actual content of the relaxation session (i.e., the deep breathing and progressive muscle exercises), most aspects of the voice used (e.g., speed, tone, and volume), and the background music (relaxing and predictable), as illustrated in some of the representative quotes in Table 6. A few participants liked the pace between each breathing exercises and muscle group (pace, 21%).

The largest proportion of limitations were related to the environment (42%), pace (24%) and content (18%). A lot of participants would have enjoyed the session better if they were lying down or on a more comfortable chair. Some suggested that the pace was not quite right (either felt too rushed or slowed down), that they would have preferred it to move at their pace instead (rather than a standard one) or to have included more variety in the exercises (as they became repetitive and predictable). Other aspects of the audiotape that participants felt could be improved included the voice (8%) saying that it was recorded too close to the microphone and the syncing between the background music and relaxation exercises could be improved (music, 8%).

Figure 16.
Bubble plot depicting the proportion of strengths and limitations for each theme in the audiotape group.

Note: The size of the bubbles represents how common each theme was, and the colours represent green for strengths and red for limitations.

Table 6.
Representative quotes for the strengths and limitations of each theme in the audiotape group.

Theme	*Strengths or limitations*	*N*	*Representative quote [Participant ID]*
Voice	Strengths	19	"The speed, pitch and tone of the voice." [p98]
	Limitations	3	"Too close to the microphone" [p22]
Music	Strengths	13	"Soft and predicable music in the background was very relaxing." [p118]
	Limitations	3	"The sync between the background music and narrator could be improved." [p51]
Pace	Strengths	3	"The length was good too as it wasn't too short or too long." [p54]
	Limitations	9	"More time in between audio instructions. Audio I listened to felt like it was rushing between steps which made it slightly less relaxing." [p80]
Environment	Strengths	8	"Lights being turned down definitely improved relaxation aspect" [p129]
	Limitations	16	"Lying down instead of sitting up" [p126]

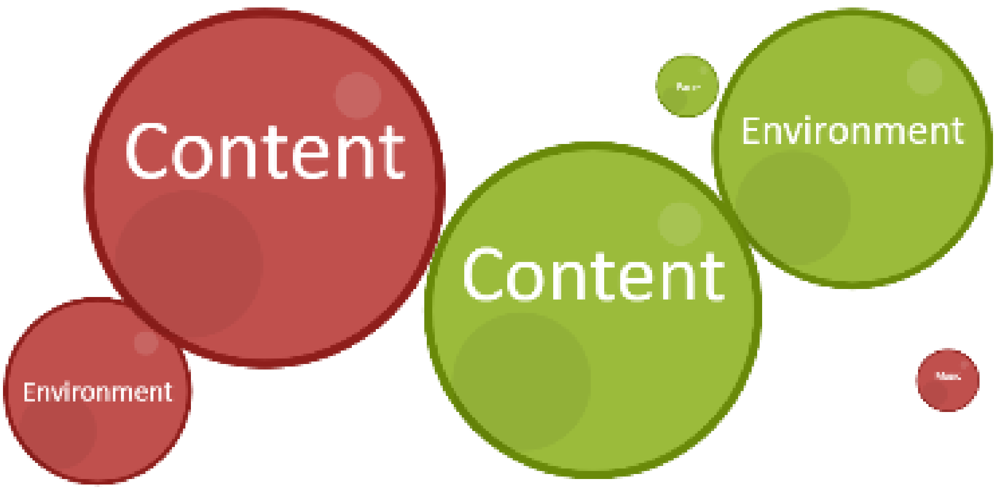
Content	Strengths	24	"The physical aspect of tensing muscles and then focusing on how relaxed they feel." [p48]
	Limitations	7	"Some different exercises included i.e., you could identify the exercise pattern after the first couple." [p100]

Control Group

The highest proportion of strengths and limitations were related to the content and environment, as illustrated in Figure 17. Participants who reported the content as a strength (57%) enjoyed sitting and read quietly and being away from their phones or responsibilities at work or home, and 40% felt that the environment was a strength (e.g., being left alone).

The largest proportion of limitation comments were related to the content of the magazine (78%) as they reported that they were too "boring" or "not varied enough" (and could be improved by providing a larger variety of magazines). 19% reported environment as a limitation, and reported wanting background music or more comfortable chairs, as illustrated in Table 7.

Figure 17.
Bubble plot depicting the proportion of strengths and limitations for each theme in the control group.



Note: The size of the bubbles represents how common each theme was, and the colours represent green for strengths and red for limitations.

Table 7.
Representative quotes for the strengths and limitations of each theme for the control group

Theme	*Strengths or limitations*	*N*	*Representative quote [Participant ID]*
Music	Limitations	1	"Maybe with some relaxing music." [p76]
Pace/timing	Strengths	1	"Relaxed pace and freedom to read in peace and undisturbed." [p9]
Environment	Strengths	17	"I liked that it was done in a quiet room, and I was alone." [p113]
	Limitations	8	"The seat I sat in while reading the magazines could have made it more comfortable to increase relaxation" [p158]
Content	Strengths	24	"The time to be able to sit down and read other forms of media that I usually don't have time to." [p45]
	Limitations	33	"I think the content of the magazines could be more interesting?" [p151]

Note: N represents the number of people who made comments in each theme.

Mediational Analyses

It was hypothesised that the effects of relaxation group on SBR would be mediated by reductions in psychological and physiological stress (Hypothesis 4). However, there were no differences between groups in SBR so mediational analysis was not conducted.

Chapter VII: Discussion

Overview

This study aimed to investigate whether a virtual human was an effective way to deliver a brief relaxation intervention to improve SBR and reduce stress after an experimental tape-stripping wound in a healthy community sample. Specifically, participants were randomly allocated to receiving a 20-minute relaxation session delivered by a Digital Human; human recorded audiotape or the control group who read magazines quietly for 20 minutes.

This chapter summarises the study's findings and interprets them in the context of existing literature. Theoretical and clinical implications will be discussed, as well as the strengths and limitations of the study. The chapter finishes with directions to explore in future research.

Findings

The findings from this study partly align with the four hypotheses and are outlined below. There were three hypotheses related to the primary outcome, SBR. First, it was predicted that SBR would be improved in the Digital Human and audiotape group compared to the control, and second, that SBR would not be different between the digital and audiotape groups. The primary hypothesis was not supported by the results; SBR was not significantly different between groups. As there were no differences between the digital and audiotape groups, the second hypothesis was supported. The final hypothesis related to SBR was that improvements in healing would be mediated by stress. This was also not supported as the null healing effects meant a mediation analysis could not be conducted.

Hypothesis three, which predicted that the Digital Human and audiotape groups would have similar psychological and physiological variables, superior to the control group, was partly supported by the findings. Some significant differences in psychological measures between groups were observed, finding that the audiotape and Digital Human had similar increases in relaxation levels, significantly greater than the control. Additionally, the audiotape had significantly reduced anxiety levels compared to the Digital Human and control group. There were no significant differences in anxiety between the digital and control groups, but the medium effect size shows that the difference could become significant in a larger sample size. The rest of the psychological measures (stress and pain) and physiological measures (HR and EDA) were not significantly different between groups, contradicting the remainder of hypothesis three.

Like the psychological and physiological secondary outcomes, the satisfaction and engagement ratings were predicted to be similar between the audiotape and Digital Human group, superior to the control. However, only the audiotape results support this hypothesis. Participants in the audiotape group were significantly more satisfied with their relaxation session than the control and Digital Human group and found their relaxation significantly more engaging than the control group. There were no differences between the Digital Human and audiotape or the digital control group.

There was no specific hypothesis regarding the open-ended responses because they were designed to explore the strengths and limitations of each delivery method. The responses provided valuable insight into salient factors for relaxation interventions, reinforcing the promising relaxation and anxiety findings of audiotape and Digital Human groups. Across the relaxation interventions, participants liked the content of the relaxation session, the background music, and the environment in which the relaxation session was conducted. The pace was a frequently mentioned limitation, with participants suggesting that they wanted the relaxation to be more personalised (e.g., choose the length and content of the sessions, use individual’s names) or have better timings between the exercises (i.e., between breathing cues or each muscle group).

Notable responses specific to the Digital Human group included its appearance and voice. Of the strength comments, participants mostly perceived the voice positively (e.g., calm, soothing and relaxing), while limitations included comments about it having “robotic tones” or jolts between sentences and breathing cues.. Comments on the appearance of the Digital Human showed that few participants liked her natural body movements (e.g., swaying, and calming mannerisms), but most comments were limitations around issues lip-syncing, and making Sam appear less "unsettling" and “robotic”.

Integration into Existing Literature

To our knowledge, this was one of the first studies to investigate the role of virtual humans in delivering relaxation interventions to improve healing and reduce stress. The findings of this study contribute to the literature in three ways: firstly, in relation to wound healing and secondly to the relaxation interventions. These two sections place the null healing and stress reduction findings (of both the relaxation interventions) into existing literature, suggesting possible factors that may account for these findings. Factors relating to wound healing, such as the short recovery “healing” period, inappropriate control group, and insufficiently stressed sample, may account for the null healing effects. Factors related to relaxation interventions, such as the insufficiently stressed sample, sample characteristics and intervention length may have undermined the effectiveness of the relaxation intervention. Despite null findings on healing and stress reduction, the virtual human was found to deliver a brief relaxation intervention and relax people, comparable to traditional human recorded audiotapes. This relaxation finding adds promise to the limited, but growing virtual human literature, and the open-ended responses provide valuable insight into the additional work needed to be made on the virtual human design to improve acceptability, satisfaction, and their potential effectiveness.

Wound Healing

Previous research explored in the earlier chapters would suggest that relaxation effectively improves wound healing (Broadbent et al., 2012; Holden-lund, 1988; Rice et al., 2001; Robinson et al., 2015). The primary hypothesis was unsupported by the unexpected findings that healing rates were similar across all groups. However, several explanations may account for the null effects of relaxation on SBR, discussed below.

The lack of effects after the relaxation may have been due to the short timing of the recovery ("healing") period. Tape stripping literature indicates that the first 60 minutes following the skin disruption is the most critical for improvements in healing (Robles et al., 2007). The current study used the same 20-minute recovery period as Robinson and colleagues (2015) did, but in Robinson's work, all groups had an additional 20-minute period of either relaxation or quiet reading prior to the tape stripping, which may have enhanced the subsequent healing. It is possible that meaningful improvements in healing between groups could have been observed in this study had healing been assessed later.

Another reason for the null findings in healing between groups may be the choice of the control group. Quietly reading magazines is often used as an active control group in research because it is a neutral activity that is not too relaxing or exciting but prevents participants from getting too bored from lack of stimulation (and inducing negative emotions; Robinson et al., 2017; Skoluda et al., 2015). However, it is questionable whether magazines are an appropriate control group for use in wound healing studies. Reading may add confounding factors (i.e., distraction, cognitive enrichment) that do not allow for a true and valid comparison of intervention effects (Law et al., 2020a). In the context of relaxation and healing, previous studies have shown mixed findings across different types of control groups. Like the current study, Gouin and colleagues' (2008) found null effects on healing between the relaxation and magazine control groups, but other relaxation studies found significant healing improvements between the intervention and control groups (Holden-lund, 1988; Robinson et al., 2015). Instead of an active control group, the remaining relaxation and wound healing studies found significant intervention effects compared with care as usual (Broadbent et al., 2012; Rice et al., 2001) or without a control group (Han, 2002).

While relaxation, satisfaction and engagement levels were lowest in the control group and were not correlated with SBR, the magazines may have resulted in similar healing to the relaxation groups in another way (e.g., distraction). These low scores indicate that participants did not find reading magazines very relaxing, satisfying or engaging (as hypothesised), but open-ended responses revealed thoughts of distraction and escapism. Many participants reported enjoying sitting and doing something easy while appreciating the time away from their phones, responsibilities at home or work, or uncertainties surrounding COVID-19. Considering the sample's demographics, most participants were younger adults studying or working, meaning that this time away from their phones and responsibilities was a likely welcome distraction. Additionally, recruitment occurred during the second year of the COVID-19 pandemic before and after a lockdown, which may have exacerbated the enjoyment and distraction of quietly reading magazines. Distraction has been previously linked with improved wound healing in previous studies (Brown et al., 2014; Miller et al., 2011), and therefore, the magazines may have acted as a distraction that could have had similar healing effects on SBR as the relaxation groups. Given possible confounding effects, reading magazines may not be an appropriate control group for experimental wound healing research..

A further complication was that the control group was more relaxed and reported more sleep than the relaxation intervention groups at baseline. Sleep is a health behaviour that has been shown to modulate wound healing indirectly; poor quality and lack of sleep slow healing, while better quality and more sleep can improve healing (Leproult et al., 1997; Veldhuis & Iranmanesch, 1988; Vgontzas et al., 1999). In tape stripping research, one night of sleep deprivation has slowed SBR (Altemus et al., 2001), illustrating the skin's susceptibility to sleep behaviours. Even though we controlled for these baseline differences statistically and used change scores, as recommended by Vickers and Altman (2001), random group differences at baseline may have contributed to the null findings in healing between groups.

A final possible reason for the lack of group differences may be that the sample had relatively low-stress levels throughout the experimental session. Therefore, participants in the current study may not have experienced healing benefits from the relaxation intervention compared to a highly stressed sample. On average, baseline PSS scores were no more than 19/40, indicating the sample was only experiencing a low to moderate amount of stress two months prior to the experimental session (Cohen, 1985). The VAS measure of psychological stress at baseline was relatively low, with no groups over 40/100, and remained low (none above 23/100) after the tape stripping procedure, indicating that stress levels were already low before the relaxation session. Consistent with several experimental wound studies, the null findings in SBR may be explainable by floor effect problems whereby low pre-intervention stress levels prevented participants from benefiting from the relaxation, as predicted (Gouin et al., 2008; Law et al., 2020a). Some research suggests that psychological interventions may only influence immune parameters when the sample is sufficiently stressed (Miller & Cohen, 2001; Morley-Fletcher et al., 2003), and this may be the case in the current findings.

The discrepancies between Robinson’s (2015) and the current study could be attributed to the differing stress levels; Robinson’s study reported slightly higher stress at baseline. As a result, participants may have found more healing benefits following the relaxation (compared to the current sample). Together, the low stressed sample makes it challenging to determine the stress reduction effects of the relaxation intervention and questions whether brief relaxation interventions are only effective in improving healing and buffering against stress in highly stressed samples.

The theory suggests that stress reduction can improve wound healing and the study hypothesised that healing would be mediated by psychological, physiological, and biological measures of stress. However, some studies have shown that psychological interventions improve healing despite having no effects on self-reported stress (Broadbent et al., 2012; Robinson et al., 2015). This may be due to poor measures of changes in stress, or this may be because other mechanisms are at work (e.g., anxiety or mood). The current study was unable to conduct an exploratory mediation analysis due to the null healing effects, so was not able to investigate the stress reduction theory further. Analysis of the saliva samples may provide further insights once completed. However, it remains inconclusive as to whether stress reduction is the mechanism behind interventions (such as relaxation) on healing. As discussed in this section, there are several factors that may have contributed to the null findings in healing and stress outcomes. These findings offer recommendations and direction for future experimental research to try tease apart the mechanisms and determine whether stress reduction is the main theory behind these effects on healing.

Relaxation Interventions

The secondary outcomes demonstrate promising effects on psychological relaxation and anxiety levels following a brief relaxation intervention delivered by a virtual human and audiotape, consistent with existing literature. However, the non-significance between groups in other psychological and physiological variables does not align with the literature. These discrepancies could be due to low pre-intervention stress levels, the characteristics of the sample (clinical or healthy community), and intervention length.

The significant increases in relaxation observed in the digital and audiotape group and reductions in anxiety in the audiotape group (compared to the control group) aligns with existing relaxation intervention literature. In particular, the findings add to the demonstrated effectiveness of PMR and deep breathing techniques in increasing psychological relaxation (Pawlow & Jones, 2002; Toussaint et al., 2021) and reducing anxiety (Holland et al., 1991; Manzoni et al., 2008; Sloman & Hons, 2002; Wilk & Turkoski, 2001.). Despite the non-significance in anxiety change scores, the medium effect size indicates that the difference between the Digital Human and control group could become significant with a larger sample size.

Existing research exploring relaxation interventions shows that deep breathing and PMR can effectively reduce stress and induce the relaxation response, as reflected by reduced sympathetic and increased parasympathetic activity (Perciavalle et al., 2017; Toussaint et al., 2021). As these studies were delivered by a human therapist or through audiotapes, the current study was the first to test these techniques on physiological outcomes when delivered by a virtual human after a tape-stripping procedure. However, contrary to the hypotheses and previous research explored in earlier chapters, changes in HR and EDA were not significantly different between the three groups, showing that physiological stress was not reduced, and the relaxation response was not induced after either of the relaxation interventions. This finding does not align with the existing literature, likely due to the current sample's low pre-intervention stress levels and the length of the relaxation intervention.

As discussed earlier, the sample had low levels of psychological stress at baseline and post tape stripping, and physiological measures of stress were low throughout the session too. The floor effect problem may again account for the lack of stress reduction effects in both psychological and physiological stress measures. Of the existing literature, a considerable number showed PMR, and deep breathing were effective for improving health outcomes when conducted with clinical patient samples (Dunford & Thompson, 2010; Kwekkeboom & Gretarsdottir, 2006; Kılıç & Parlar, 2021; Perciavalle et al., 2017; Warsono, 2020; Wilk & Turkoski, 2001). Patients deal with a range of stressors (e.g., illness-related, financial concerns, isolation, pain, loss of independence) that can accumulate and put them at a higher risk of experiencing chronic stress (Lusk & Lash, 2005; Mishel, 1984; Volicer, 1977).

In a wound-healing context, a 4-week ISMP intervention effectively reduced psychological stress, EDA, respiratory rate, and muscle tension in patients with peptic stomach ulcers (as described in Table 1). The current study was the first to measure EDA and HR measures following an experimental wound (tape-stripping), and possible differences between findings could be due to the type of sample, their baseline stress levels or severity of the wound. Like the wound healing section above, relaxation interventions may also be more effective in reducing physiological measures (and inducing the relaxation response) in a highly stressed sample (i.e., a clinical rather than a healthy community sample) or with more intense and invasive wounds (i.e., in surgical wound rather than a tape-stripping wound).

Another factor to consider in the null stress reduction finding and to help account for discrepancies with previous relaxation research is the length and number of the intervention. Many of the effective relaxation interventions conducted in healthy samples were completed daily or weekly for months, as opposed to a one-off session (Ospina et al., 2007; Pawlow & Jones, 2002). For relaxation to effectively buffer against stress and act as an adaptive mechanism (i.e., reduce sympathetic and increase parasympathetic activity), people may need to engage in repeated and consistent use of these techniques over time (Dusek & Benson, 2009; Park et al., 2013). It is possible that the brief relaxation session in the current study just was not long enough to observe any meaningful changes in these physiological measures. Given the high satisfaction rating and relaxation improvements, it would be feasible to trial similar relaxation exercises in a longer intervention (e.g., short daily sessions or more extended weekly sessions across months). This would help understand whether relaxation can show meaningful improvements in healthy participants given consistent and repeated practice.

Virtual Humans

The experimental design factors (recovery period, inappropriate control group, insufficiently stressed sample, sample characteristics and intervention length) described above may explain why there were no observed differences in healing and stress reduction between the two relaxation intervention groups and the control. Despite these null effects, the current study adds to the growing evidence surrounding virtual humans' ability to deliver health and psychological interventions (Gardiner et al., 2017; Hudlicka, 2013; Loveys et al., 2021; 2022). Specifically, the findings show that a virtual human has comparable psychological relaxing effects to a traditional human recorded audiotape. Medium effect sizes in anxiety reductions also suggest that the differences between the Digital Human and the control group could become significant given a larger sample size.

While people were more relaxed in the Digital Human group, they reported lower satisfaction ratings than the audiotape group. A recent CSBM feasibility study found that satisfaction, acceptability, and engagement did not differ between delivery methods (self-guided manual, Digital Human, and human therapist), but that study was not powered to find differences (Loveys et al., 2022). Factors associated with technological limitations, participant expectations or uncertainty around virtual humans likely played a role in the current study's poor satisfaction findings and discrepancies with recent work.

The open-ended responses revealed that many participants liked our Digital Human's (Sam) voice as they reported that she was "calming" and had a "soothing tone", but this is likely because she used and manipulated a real human voice. Participants raised issues concerning the appearance and lip-syncing of the Digital Human and feelings of uncertainty (e.g., they expected Sam to be interactive or were unsure about the novel form of technology). These limitations likely outweighed the strengths of the voice alone, and as a result, the Digital Human still provided significant relaxing effects (from the voice), but issues and uncertainties in the technology could have contributed to the poor satisfaction scores. Together, there are promising relaxation results which build upon some of the existing virtual human literature. However, satisfaction and the additional open-ended responses demonstrate that more work is needed to improve the acceptability and effectiveness of virtual humans, particularly in a stress reduction context.

Theoretical Implications

Developing and testing novel and effective ways to deliver health interventions and information to improve health outcomes has become the focus of the digital health research space in the past decade. This RCT aimed to investigate the effects of a virtual human delivering a brief relaxation intervention on stress and healing. Despite the null effects on healing and stress reduction, several theoretical and clinical implications for virtual humans have emerged from the other secondary outcome findings.

A critical theoretical implication is related to the uncanny valley, a salient theory when working with artificial agents, such as virtual humans. Two previous studies using Digital Humans to deliver psychological interventions did not report any uncanny valley effects. The first was a large study on social closeness and emotional support seeking, and the appearance and behavioural realism of the Digital Humans were not perceived as aversive, suggesting that the uncanny valley had not been crossed (Loveys et al., 2021). In the delivery of CSBM, the second study did not report an uncanny valley effect either, likely because the deep breathing exercise played by the Digital Human in Loveys and colleagues (2022) study used a human voice recording. As the current study delivered a complete relaxation session using a Digital

Human’s voice and embodiment and found reported feelings of Sam appearing "creepy", "eery", and "unsettling”. In particular, the mismatch between the mouth movement and the Digital Human’s voice (i.e., lip-syncing errors) reported likely acted as the "abnormal" feature that induced more negative feelings in the open-ended responses, indicating the presence of the Uncanny valley effect (Mori et al., 2012). This finding adds to the Uncanny valley theory by highlighting that the appearance, voice, and matching the two through lip-syncing plays a critical role in virtual humans' acceptability (and potential effectiveness) in delivering relaxation interventions. Together, these results will be useful to guide future virtual human design, particularly for use in relaxation or stress reduction contexts.

Clinical Implications

Real-life uptake of e-health and mental health interventions remains a challenge (McNamee et al., 2016; Murray et al., 2016). Improving the engagement and satisfaction of virtual humans is a critical part of successful implementation and uptake (and effectiveness). The improvements in relaxation and promising trends in reducing anxiety demonstrate the potential effectiveness of a brief relaxation intervention delivered by a virtual human (comparative to an audiotape). The open-ended responses provided valuable insight and suggestions to improve the delivery of virtual humans. Specifically, some participants suggested personalising the pace and length (i.e., the individual choosing how fast, slow, and long the session is), using the individual's name, and the ability to choose the content of exercises. These comments highlight issues that need to be addressed before being put into clinical practice.

In traditional relaxation interventions delivered by a human therapist, the pace is matched with the patient as a part of a contingent process. The clinician matches the pace of the instructions to the patient needs and performance in real-time. In PMR, this is a response contingent process whereby the therapist waits for the patient to signal when they have reached tension and relaxation of each muscle group before continuing around the body (Paul & Trimble, 1970). However, the audiotape and Digital Human video instructions were program contingent as they remained at the same set pace regardless of the individual. This process increases incongruences, which may frustrate or stress patients more by making them feel rushed or slowed (Lehrer et al., 1986). Some incongruence was reflected in the open-ended responses, as some participants mentioned feeling rushed or slowed down by the set timings between each group or breathing cues. In line with prior relaxation research, these responses underline the role and importance of personal preference (particularly the pace, timing, and length) in relaxation delivery and implementation. Designing virtual humans to adjust the pace and timing of relaxation exercises could help improve their effectiveness and uptake outside of an experimental context.

Strengths

Several strengths allow the current study to provide meaningful and novel contributions to the literature. This study builds on previous feasibility and acceptability studies by investigating the effectiveness of upcoming virtual humans in a wound healing context by adopting a randomised controlled trial design. RCT studies are regarded as the 'gold standard' for research (Kaptchuk, 2001), and the current study was conducted within a controlled experimental setting (e.g., following TEWL measurement and salivary collection guidelines).

While there were no significant differences between the Digital Human and control group in SBR, the secondary outcomes (relaxation, satisfaction, engagement) and open-ended questions provided valuable insight into the role of the virtual humans in delivering relaxation. In particular, the inclusion of open-ended questions provides a rich and meaningful understanding of a virtual human’s ability to deliver relaxation instructions. These responses can help guide future virtual human delivered health interventions, explain findings (or lack of) in the health outcomes, and allow for improvements in future iterations. For example, while people found the Digital Human to be just as relaxing as the audiotape, a few open-ended comments (voice, appearance, mismatch in lip-syncing) were reported as limitations, which helped to understand why the relaxation improvements were not associated with higher satisfaction and engagement ratings.

Another strength was that the study reduced relaxation expectancy effects. Unlike the study conducted by Robinson and colleagues (2015), the control condition (reading magazines) was advertised as a type of relaxation intervention, meaning that participants were expecting to be relaxed, regardless of the group they were allocated to. As a result, the significant differences in relaxation change scores reflect actual relaxation responses instead of rating the Digital Human and audiotape condition higher, knowing that they are the "intervention".

Limitations

Several limitations need to be considered alongside the study's strengths. First, the tape stripping wound is only minor, not reflective of a real-life clinical or chronic wound and is sensitive to environmental conditions (compared to other experimental wound types). TEWL measurement errors reduced the number of data available for SBR analysis, therefore underpowering it. Whilst TEWL guidelines were followed, unexpected changes in conditions due to covid (e.g., wearing a mask, social distancing) and fluctuations in temperature over the extended time of the study may have limited the number of valid TEWL measurements. Temperature and humidity are particularly salient environmental factors that can influence wound healing and TEWL measurements (Denda et al., 2000; Rogers, 2001). Given the variation in room conditions, it is likely that room humidity and temperature affected TEWL readings. The study was also limited by not directly measuring room temperature or humidity, as these could have been added as covariates in the SBR analysis.

Due to constraints in the time frames and technology, the appearance and embodiment of the Digital Human were not able to be customised or be delivered as a live interaction. The default appearance of the Digital Human was a European female, which is not representative of people from other ethnicities, genders, or cultures. Not being able to choose or match the embodiment to the participants can be considered a limitation, as it may have affected satisfaction scores. Additionally, due to time constraints during the development process, the current study could only use a video recording of a programmed Digital Human (rather than an interactive one, like previous feasibility studies; Loveys et al., 2020; 2021). This can limit the comparisons and ability to accurately assess the impact of the Digital Human.

Future research

Several areas of interest could be explored further in future studies. For example, the research could investigate the ability of virtual humans to deliver relaxation and improve healing in a highly stressed sample. The current sample was low to moderately stressed at baseline, and their healing and stress levels (psychological and physiological) may not have benefited from the relaxation compared to a more stressed sample. Stress could be manipulated by using an acute experimental stressor such as the Trier Social Stress Test, which has been shown to impair SBR in previous tape stripping studies (Altemus et al., 2001; Robles et al., 2007). Alternatively, studies could specifically recruit participants who identify as highly distressed or patients with surgical or chronic wounds. With sufficiently stressed participants, it would be easier to test the effectiveness of virtual humans in delivering relaxation and reducing stress (and test their stress-reducing ability, if it exists).

Considering the significant improvements in relaxation and anxiety but non-significant stress-reducing effects for intervention groups, future research could build off the current study by addressing the factors that may have accounted for the null effects. For example, it could be worthwhile using a non-active control (e.g., sitting quietly or waitlist control) to isolate the true intervention effects of the relaxation. Additionally, the one-off 20-minute exercise may not have been long enough to observe meaningful effects on physiological stress indices in either intervention group. Instead, the same relaxation exercises could be tested daily with a more serious wound (such as a punch biopsy) across days or weeks while it heals. This could help determine and understand the time frames and relaxation length needed to provide meaningful health improvements.

Future research could also utilise the interactive capabilities of virtual humans in relaxation interventions, as the current study has demonstrated the importance of personalisation and tailoring in the relaxation experience. While the Digital Human used in the study was a pre-recorded video delivering the relaxation instructions, their interactive capabilities could see future studies to trial a more interactive Digital Human (where users can interact with speech or text input) while adapting pace and timings with the patient. However, more work is needed to improve the lip-syncing and voice matching technology to reach this stage.

Finally, virtual human research should include measures of familiarity to determine whether novelty effects exist, and whether they account for virtual humans' effectiveness and acceptability. For example, it would be interesting and useful to understand whether the people who reported feeling confused and uncertain about the Digital Human's purpose and capabilities had interacted with or seen a digital (or other types of virtual human) before. Those more familiar with virtual humans may have been more likely to feel satisfied with the delivery method, as opposed to those who were less certain. Future research could control for possible novelty effects with a familiarity check or provision of a brief introduction to the virtual human prior to the intervention.

Conclusions

The growing body of literature shows that virtual humans have promise for delivering eHealth interventions. This was the first RCT to test the healing, psychological and physiological effects of relaxation delivered by a virtual human compared to other conditions. Results showed no significant effects of the delivery method on wound healing or stress reduction, but secondary outcomes showed the ability of a virtual human to relax people, comparable to an audiotape. The study explored factors that may have accounted for the null effects on healing and stress reduction and provides future experimental research design recommendations to address these. The additional open-ended feedback highlighted areas to improve the design and effectiveness of virtual humans in delivering stress reduction interventions.

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Appendices

Appendix A

Auckland Health Research Ethics Committee Approval Letter

AUCKLAND HEALTH RESEARCH ETHICS COMMITTEE (AHREC)

03/03/2021

Dr Elizabeth Broadbent

Re: Application for Ethics Approval (Our Ref. AH21981): Approved

The Committee considered your application for ethics approval for the study entitled "**Effects of Relaxation on Wound Healing**".

We are pleased to inform you that ethics approval has been granted.

The expiry date for this approval is **03/03/2024**.

Amendments to the approved project: Should you need to make any changes to the approved project, please follow the steps below:

- Send a request to the AHREC Administrators to unlock the application form (using the Notification tab in the Ethics RM form).
- Make all changes to the relevant sections of the application form and attach revised documents (as appropriate).
- Change the Application Type to "Amendment request" in Section L.
- Add a summary of the changes requested in the text box.
- Submit the amendment request (PI/Supervisors only to submit the form).

If the project changes significantly, you are required to submit a new application.

Funded projects: If you received funding for this project, please provide this approval letter to your local Faculty Research Project Coordinator (RPC) or Research Project Manager (RPM) so that the approval can be notified via a Service Request to the Research Operations Centre (ROC) for activation of the grant.

The Chair and the members of AHREC would be happy to discuss general matters relating to ethics approvals. If you wish to do so, please contact the AHREC Ethics Administrators at ahrec@auckland.ac.nz in the first instance.

Additional information:

- Do not forget to fill in the 'approval wording' on the PISs, CFs and/or advertisements, using the date of this approval and the reference number, before you use the documents or send them out to your participants.

All communications with the AHREC regarding this application should indicate this reference number: **AH21981**.

AHREC Administrators

Auckland Health Research Ethics Committee

Appendix B

Study Recruitment Poster

THE UNIVERSITY OF AUCKLAND NEW ZEALAND

MEDICAL AND HEALTH SCIENCES

EFFECTS OF RELAXATION ON WOUND HEALING

Are you over the age of 18, fluent in English, able to see/hear without difficulty, and keen to help on a study investigating relaxation delivery methods on health and skin recovery? Then we would love your participation in our research!

You will be provided with a $30 Westfield gift voucher as compensation for your participation. Your involvement would include one 90-minute session at the University of Auckland, Clinical Research Centre, Grafton Campus.

For further information, please contact:

Isabella Pickering, Master's student

Department of Psychological Medicine

University of Auckland

ipic652@aucklanduni.ac.nz

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE ON 03/03/2021 FOR THREE YEARS. REFERENCE NUMBER AH21981.

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Appendix C

Participant Information Sheet

MEDICAL AND HEALTH SCIENCES

Faculty of Medical and Health Sciences

The University of Auckland

Private Bag 92019

Auckland 1142

New Zealand

Effects of Relaxation on Wound Healing

PARTICIPANT INFORMATION SHEET

You are invited to take part in a study investigating the effects of different relaxation delivery methods on wound healing. This project is run by Isabella Pickering, a Master's student in the Department of Psychological Medicine at the University of Auckland, supervised by Professor Elizabeth Broadbent from the Department of Psychological Medicine at the University of Auckland and co-supervised by Mikaela Law (PhD student) and Kate Loveys (PhD student) from the Department of Psychological Medicine at the University of Auckland.

It is important to read this document carefully so that you can make an informed decision about whether you would like to participate.

Purpose of the study: This study aims to evaluate the effects of different relaxation delivery methods on wound healing, measured by skin barrier recovery.

Eligibility: To participate in this study, you must be over the age of 18, speak, read, and write in fluent English and be able to see and hear without difficulty. You will not be able to participate in this study if you are allergic to adhesive tape, have any inflammatory skin diseases/immunological-related health problems, are taking medication that affects immune functioning (e.g., prednisone), are pregnant, over the age of 60 or have hearing difficulties or vision loss.

Procedure: If you choose to participate in this research, you will be asked to complete one 90-minute session at the University of Auckland's Clinical Research Centre in Grafton. You are encouraged to talk with whānau or support people before participating if appropriate. Following salivary procedures and to reduce interference in the TEWL measures, we ask you not to drink caffeine, juice or alcohol 18 hours before the study and not eat, shower, exercise or apply moisturiser in the hour before the study.

Relaxation. You will be randomly assigned to one of three types of relaxation delivery methods: magazines, audiotapes, or a digital human. Relaxation has shown to be effective at reducing stress and improving immune function. All relaxation sessions will take approximately 20 minutes. The relaxation session that is allocated to you will be completed after the tape-stripping procedure and during the recovery period to determine how it influences the rate at which your skin barrier recovers. During the 20-minute recovery period you will be video recorded using an external webcam. The researcher will not be in the room during this recovery period but will be nearby if you need assistance.

Tape stripping: The study requires you to undergo a simple and non-invasive tape-stripping procedure on your forearm. During this procedure, tape will be applied to the skin on your forearm in three $1cm^2$ areas just below your elbow to remove the topmost layer of your skin. This will be repeated several times until your skin barrier function reaches below a certain threshold. To ensure the right level of skin disruption is achieved, a small probe will be pressed gently against your skin for a few minutes. After a 20-minute recovery period, your skin barrier function will again be tested using this probe to examine how much your skin has recovered.

Biological measures. Saliva samples will be collected at three time-points throughout the study: at baseline, after the tape stripping procedure and after the recovery period. These saliva samples will be analysed to examine levels of cortisol and alpha-amylase (hormones). The samples will be stored in salicap containers labelled only with your participant ID number in a secure lab in the University of Auckland at -20 degrees Celsius for up to 2 years. The samples will be sent overseas on dry ice to the University of Vienna (Austria) for analysis by a specialist laboratory. These samples will not be used for anything other than the purpose of this study. After the salivary samples have been analysed, they will be disposed of appropriately, and not used for any future research.

Physiological measures. During the experimental session you will be wearing a wrister sensor to continuously measure heart rate and skin conductance.

Questionnaires. During the experimental session you will be asked to complete a series of questionnaires related to your demographics, health behaviours, levels of stress, pain, anxiety and relaxation and opinions on relaxation delivery.

Audiovisual Data. There will be an external webcam set up to video record you during the 20 minute recovery period to see whether your wound was touched or interfered with (as this can effect how your wound heals). This recording will be stored on a single user, password protected computer and labelled with your participant number only to ensure confidentiality.

Your rights as a participant: Participation in this study is entirely voluntary. If you choose to participate, you can change your mind at any time, including during a session, without giving a reason and without any negative consequences. You may also withdraw your data up to two weeks after completing the study, in which case the data will be securely destroyed. You will be given a copy of this document to keep.

Koha: You will receive a $30 Westfield gift voucher at the end of the session as compensation for agreeing to participate in this research. You will receive this irrespective of whether you withdraw during the study.

Risks and discomforts: The procedures outlined in this protocol are minimally invasive and have been performed in other research settings. The tape-stripping procedure may cause slight discomfort and redness of the skin, but this should disappear within 24 hours. If you have an allergy to cello tape or adhesives, an inflammatory skin disease or are taking medication that affects immune functioning, you should not take part in this study. If skin irritation persists, you should contact University Health Services on 09 923 7681 (for University of Auckland students) or your GP (normal charges will apply) to make an appointment with a doctor or contact the researchers to organise to see the study dermatologist, Dr. Paul Jarrett.

Your researcher is not medically trained and therefore is unable to make any clinical observations about your physiological measures or mental states during the sessions. However, if any abnormal physiological or psychological recordings are made, you will be informed and encouraged to contact the appropriate experts.

Cultural Support: If you require Māori cultural support, talk to your whānau in the first instance. Alternatively, you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext 2324. If you have any questions or complaints about the study, you may contact the Auckland and Waitematā District Health Boards Māori Research Committee or Māori Research Advisor by phoning 09 486 8920 ext 3204.

Data storage: All data (including questionnaires, physiological, and wound healing measurements) and video recordings (from the 20 minute intervention period) will be stored on a single user, password protected computer in the University of Auckland, Department of Psychological Medicine for six years, after which all data will be disposed of by permanently deleting.

Confidentiality: All personal information will remain strictly confidential and no material that could personally identify you will be used in any report on this study. All questionnaire, wound healing, physiological measures and video recordings are labelled with a participant number only, so that your identity is kept confidential. Participant names and contact details will only be linked to the data via a master sheet that will be stored in a locked file, separately from the data. Only the researcher will have access to the password protected data files that contain participant data (including the protected folder for video recordings).

Research publications and presentations from the study will not contain any information that could personally identify you. We will publish the results but not the data itself. The purpose the data is collected is to investigate the research question and publish results in a journal paper and/or presentation.

Results: A summary of the results of this study in non-academic language will be sent to you if you wish. As it takes some time to analyse the results of studies, it may be more than a year after your participation that you receive this information.

Technology confidentiality: As this study involves the use of some technology by Soul Machines Limited, we do ask that you do not discuss your experiences during the Research with anyone. As this research forms part of Soul Machines' world leading research program, we are insisting that you do not engage in media interviews or discussion, or blog or make any other form of account of your experience, including on your own social media. Accordingly, before you take part in the Research, we ask that you sign the acknowledgments related to technology confidentiality outlined in the consent form. It is a condition of your participation in the Research that you accept the acknowledgments outlined below. If you do not wish to sign the acknowledgments, you are free to withdraw from the Research. If you have any questions, please email privacy@soulmachines.com. You will be asked to acknowledge and agree to the following:

a. I will not make any video and/or audio recordings or take any photographs of the Research or my participation in the Research.

b. I will not publish any articles (including any video and/or audio content) or make or authorize any public comments relating to or referring to the Research or my participation in the Research.

c. I do not work for or contribute to any media organization.

d. I have had the opportunity to ask questions and have them answered to my satisfaction.

Contact details: We appreciate the time you have taken to read this information. If you have any questions, please contact:

Isabella Pickering

Masters student

Department of Psychological Medicine

The University of Auckland

Private Bag 92019, Auckland 1142

Email: ipic652@aucklanduni.ac.nz

Alternative contacts:

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Professor Sally Merry

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Email: s.merry@auckland.ac.nz | Telephone: (09) 923 6981

For concerns of an ethical nature, you can contact the Chair of the Auckland Health Research Ethics Committee at ahrec@auckland.ac.nz or at 373 7599 x 83711. or at Auckland Health Research Ethics Committee, The University of Auckland, Private Bag 92019, Auckland 1142

Approved by the Auckland Health Research Ethics Committee on 3/3/2021 for three years. Reference number AH21981.

Appendix D

Consent Form

MEDICAL AND HEALTH SCIENCES

Faculty of Medical and Health Sciences

The University of Auckland

Private Bag 92019

Auckland 1142

New Zealand

Effects of Relaxation on Wound Healing

PARTICIPANT CONSENT FORM

This form will be stored for a period of 6 years.

Researchers: Dr. Elizabeth Broadbent (Supervisor), Mikaela Law (Co-Supervisor, PhD student), Kate Loveys (Co-Supervisor, PhD student) and Isabella Pickering (Master's student).

- I have read the Participant Information Sheet and have understood the nature of the research.
- I understand that participation in this study is voluntary and will take me approximately 90 minutes to complete.
- I know that I can withdraw my participation at any time without giving an explanation and I can withdraw any data traceable up to two weeks after completing the study if I wish, in which case the data will be securely destroyed.
- I know who to contact if I have any questions about the study.
- I have had the opportunity to ask questions and have them answered to my satisfaction.
- I have had the opportunity to talk with whānau before participating in the study if appropriate.
- I understand that my responses will be used for data analyses.
- I understand that the overall results may be published in a scientific journal but will not include any information that could identify me.
- I understand that participation in the study is confidential and that no material which could potentially identify me will be used in any reports or shared with any individual or organisation.
- I understand that during the experimental session, some of my responses will be video-recorded.
- I understand that during the experiment I will be subjected to a tape stripping procedure which may cause slight discomfort and redness of the skin, but this should disappear within 24 hours. If skin irritation persists, I understand I can contact University Health Services on 09 923 7681 to make an appointment with a doctor or contact the researchers to organise to see the study's dermatologist.
- I understand that there is cultural support available by contacting the administrator for He Kamaka Waiora (Māori Health Team) on 09 486 8324 ext 2324.

- I understand that my salivary samples will be stored securely at the University of Auckland at -20 degrees Celsius and will be sent to Austria for analysis after which they will be disposed of, and not used for any future research.
- I understand that throughout the experiment, I will complete a series of questionnaires, which include answering questions about my demographics, health behaviours, levels of stress, pain, anxiety and relaxation and opinions on relaxation delivery.
- I understand that any audiovisual data collected by the technology used in this study will not be stored or analysed in any way by the researchers or the Soul Machines program.
- I agree to the terms related to technology confidentiality. Specifically, I acknowledge and agree that I will not make any video and/or audio recordings or take any photographs of the research or my participation in the research. I will not publish any articles (including any video and/or audio content) or make or authorize any public comments relating to or referring to the research or my participation in the research. I do not work for or contribute to any media organization.
- I understand that the research data (including questionnaires, video-recordings, physiological, and wound healing measurements) will be stored securely in the University of Auckland, Department of Psychological Medicine for six years, after which it will be disposed of by shredding/deleting according to whether it is hard copy or electronic. Participant names will only appear on the consent form, which will be coded with a participant identification number so that your identity is kept confidential on all questionnaire, physiological and wound healing data files.
- I am not aware of any reason why I should not participate in this research.
- I am aware that by taking part in this study I will be given a $30 Westfield voucher as koha for agreeing to take part in this research, irrespective of whether I complete the study.

I agree to take part in this research.

Name...

Signature...

Date.......................................

☐ I wish to receive a summary of the research findings.

Please email me at: ....

If you have any questions, please feel free to email the researcher at jpic652@aucklanduni.ac.nz

For concerns of an ethical nature, you can contact the Chair of the Auckland Health Research Ethics Committee at ahrec@auckland.ac.nz or at 373 7599 x 83711, or at Auckland Health Research Ethics Committee, The University of Auckland, Private Bag 92019, Auckland 1142

Approved by the Auckland Health Research Ethics Committee on 3/3/2021 for three years. Reference number AH21981

Appendix E

Study Questionnaires

THE UNIVERSITY OF AUCKLAND NEW ZEALAND | MEDICAL AND HEALTH SCIENCES

Relaxation and wound healing study

SCREENING QUESTIONNAIRE

Thank you for showing an interest in participating in this study. The following screening questionnaire is designed to see if you are eligible to complete the experimental session of the study. It will take about 2 minutes to complete. When you have completed it please return it by email to jpic652@aucklanduni.ac.nz

Note: Completing this questionnaire gives no obligation to complete the experiment.

Screening Questionnaire (Please tick your answer)

Are you aged over 16? ☐ Yes ☐ No

Are you aged over 60? ☐ Yes ☐ No

Are you fluent in the English Language? ☐ Yes ☐ No

Do you have hearing difficulties? ☐ Yes ☐ No

Do you have vision loss? ☐ Yes ☐ No

Do you have any allergies to skin adhesives or tape? ☐ Yes ☐ No

Do you have an inflammatory skin disorder *(e.g., eczema, rosacea, or psoriasis)?* ☐ Yes ☐ No

Are you pregnant? ☐ Yes ☐ No

Do you take regular medication? ☐ Yes ☐ No

If so, please describe ____

Name____________________________

Contact email_____________________________

Contact phone number ____________________________

Thank you for your time. Please return the complete questionnaire by email to

jpic652@aucklanduni.ac.nz

Date	
ID	

THE UNIVERSITY OF AUCKLAND NEW ZEALAND | MEDICAL AND HEALTH SCIENCES

Baseline Questionnaire

This questionnaire is designed to gather some background information on your demographics and health-related behaviours, as well as your feelings and mood. All the information you give us is confidential to the researchers and will only be used for the purposes of the study.

For all these questions there are no right or wrong answers- an answer is correct if it is true for you. We are most interested in your own opinion. Please choose the response that best fits with your circumstances.

Thank you for your help with this study.

Date	
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Demographics Questionnaire

Please answer the following questions by filling in the blanks or ticking the boxes that best correspond to you.

1. What is your gender?

☐ Female

☐ Male

☐ Non-Binary/Other

2. How old are you? ___________

3. Height ___________cm

4. Weight _________kg

5. What ethnic group do you belong to? (check all that apply)

☐ New Zealand European/Pakeha

☐ Maori

☐ Samoan

☐ Cook Island Maori

☐ Tongan

☐ Niuean

☐ Chinese

☐ Indian

☐ Other: Please Specify ________________________________

6. What is your highest level of completed education?

☐ Secondary school

☐ Technical or trade certificate

☐ University or polytechnic diploma

☐ Undergraduate University degree

☐ Postgraduate University degree

☐ None of the above

7. What is your current employment status?

☐ Employed full time (40 or more hours per week)

☐ Employed part time (up to 39 hours per week)

☐ Student

☐ Not currently employed

Date	
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Health-Related Behaviours

1. During the past three months how often have you drunk alcohol, on average?

- ☐ Not at all
- ☐ Less than once a month
- ☐ 1-3 times a month
- ☐ 1-2 times a week
- ☐ 3-6 times a week
- ☐ Every day

2. On days when you did drink alcohol in the last three months, how many drinks did you have on an average day?

- ☐ 1-2 drinks
- ☐ 3-4 drinks
- ☐ 5-6 drinks
- ☐ 7-10 drinks
- ☐ 11 or more drinks

3. During your average week, how days do you engage in 30 minutes or more of physical activity (e.g., going for a walk or run, going to the gym, swimming)?

- ☐ Never
- ☐ 1 day
- ☐ 2 days
- ☐ 3 days
- ☐ 4 days
- ☐ 5 days
- ☐ 6 days
- ☐ Every day

4. During the past week, how would you rate your diet?

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

5. Do you currently smoke?

- ☐ Yes. On an average day I smoke _______ cigarettes

Date	
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☐ No, not anymore. I quit smoking ______________ ago

☐ No, I have never smoked

6. Are you currently on any regular medication Yes/No

If yes, please indicate the name of the medication(s)

____

____

____

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

7. During the past month, what time have you usually gone to bed at night?

__________ O'clock

8. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

___________ minutes

9. During the past month, what time have you usually gotten up in the morning?

____________ O'clock

10. During the past month, how many hours of actual sleep did you get per night? (this may be different than the number of hours you spent in bed)

___________hours of sleep per night

11. During the past month, how would you rate your quality of sleep?

☐ Very bad

☐ Fairly bad

☐ Fairly good

☐ Very good

The following 2 questions are for females only.

1. On what date did you last experience menstrual bleeding?

____

2. Are you currently using hormonal contraceptives? Yes / No

If yes, please indicate the name of the medication.

____

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The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate how often you felt or thought a certain way by circling the appropriate number.

	Never	Almost Never	Some-times	Fairly Often	Very Often
1- In the last month, how often have you been upset because of something that happened unexpectedly?	1	2	3	4	5
2- In the last month, how often have you felt that you were unable to control the important things in your life?	1	2	3	4	5
3- In the last month, how often have you felt nervous and "stressed"?	1	2	3	4	5
4- In the last month, how often have you felt confident about your ability to handle your personal problems?	1	2	3	4	5
5- In the last month, how often have you felt that things were going your way?	1	2	3	4	5
6- In the last month, how often have you found that you could not cope with all the things that you had to do?	1	2	3	4	5
7- In the last month, how often have you been able to control irritations in your life?	1	2	3	4	5
8- In the last month, how often have you felt that you were on top of things?	1	2	3	4	5
9- In the last month, how often have you been angered because of things that were outside of your control?	1	2	3	4	5
10- In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	1	2	3	4	5

Date	
ID	

Please rate your current level of stress on the scale below by putting an X on the appropriate place on the line.

Not at all stressed

Extremely stressed

Please rate how much pain you are currently experiencing on the scale below by putting an X on the appropriate place on the line.

No sensation of pain

Most sensation of pain imaginable

Please rate how anxious you currently feel on the scale below by putting an X on the appropriate place on the line.

Not at all anxious

Very anxious

Please rate how relaxed you currently feel on the scale below by putting an X on the appropriate place on the line.

Not at all relaxed

Very relaxed

Date	
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Post-Tape-Stripping Questionnaire

All the information you give us is confidential to the researchers and will only be used for the purposes of the study.

For all these questions there are no right or wrong answers- an answer is correct if it is true for you. We are most interested in your own opinion. Please choose the response that best fits with your circumstances.

Thank you for your help with this study

Date	
ID	

Please rate your current level of stress on the scale below by putting an X on the appropriate place on the line.

Not at all stressed — Extremely stressed

Please rate how much pain you are currently experiencing on the scale below by putting an X on the appropriate place on the line.

No sensation of pain — Most sensation of pain imaginable

Please rate how anxious you currently feel on the scale below by putting an X on the appropriate place on the line.

Not at all anxious — Very anxious

Please rate how relaxed you currently feel on the scale below by putting an X on the appropriate place on the line.

Not at all relaxed — Very relaxed

Date	
ID	

THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND

MEDICAL AND HEALTH SCIENCES

Post-Recovery Questionnaire

All the information you give us is confidential to the researchers and will only be used for the purposes of the study.

For all these questions there are no right or wrong answers- an answer is correct if it is true for you. We are most interested in your own opinion. Please choose the response that best fits with your circumstances.

Thank you for your help with this study

Date	
ID	

Please rate your current level of stress on the scale below by putting an X on the appropriate place on the line.

Not at all stressed

Extremely stressed

Please rate how much pain you are currently experiencing on the scale below by putting an X on the appropriate place on the line.

No sensation of pain

Most sensation of pain imaginable

Please rate how anxious you currently feel on the scale below by putting an X on the appropriate place on the line.

Not at all anxious

Very anxious

Please rate how relaxed you currently feel on the scale below by putting an X on the appropriate place on the line.

Not at all relaxed

Very relaxed

Date	
ID	

Relaxation Delivery

This section will ask some questions on how you felt about the delivery of the relaxation session you just completed. There are no right or wrong answers – an answer is correct if it is true for you.

1. How satisfied were you in the delivery of this relaxation session? Please indicate your response by marking an X anywhere along the line below.

Not at all satisfied —————————— Very satisfied

2. How engaging was the delivery of this relaxation session? Please indicate your response by marking an X anywhere along the line below.

Not at all engaging —————————— Extremely engaging

For the next couple of questions, please provide a written response that is true to your experience.

3. What did you like about the delivery of the relaxation session?

4. How do you think the delivery of the relaxation session could be improved?