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PERSPECTIVE PIECE

METHODOLOGICAL ISSUES OF USING PLACEBOS IN INTERVENTIONS BASED ON DIGITAL TECHNOLOGY

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Background/Aims: Use of placebo is the ideal for comparison in clinical trials to reduce biases. With digital technology being used more frequently in healthcare interventions, how do we determine the placebo effect where interventions exploit technology? If placebo in medicine is traditionally defined by a lack of pharmacological agents, how might we begin to move towards controlling for effects of digital technology?

Method: This paper explores the traditional placebo effect and discusses its impact in healthcare contexts with digital technology with reference to a particular trial. Different meanings of placebo in the context of evaluating technology suggest new challenges and positive consequences.

Results: Methodological considerations are discussed, which enabled the development of a placebo-controlled evaluation of a digital technology in healthcare and rehabilitation.

Conclusion: Digital placebo was controlled in our trial by employing technology across all groups in the absence of evidence-based practice and shows how to control for unknown and hidden effects of technology.

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Introduction

As digital technology becomes more personalized[1,2] and is able to record and represent richer information about the body, the demands we place upon it in trials and in medicine will increase. Digital technology in health care settings is already set to increase in three ways: a) wireless sensing b) sequencing the genome and c) imaging and printing organs.[3] These will enable further capture and investigation of individual data such as blood glucose or blood pressure, or capturing responses to therapy in real-time.[3] As the volume of research with digital technology and mobiles increases, methodology will need to adapt and become more robust. Where possible, interventions evaluated using the gold standard of double blind randomized controlled trials often employ placebos as an effective countermeasure to context and subjectivity. Placebo is the purposeful null effect of an intervention and is usually employed in opposition to an active technology e.g. therapy, within a clinical trial. However, use of placebo in interventional trials where digital technologies such as mobiles are used, requires evaluation, and as yet there is no clearly established methodology. In complex interventions with digital technology, rigorous evaluation is needed, and traditional placebo alters due to demands placed on trial fidelity.

This paper is based on our experiences and reflections from our own evaluation of placebo during the development of an NIHR feasibility trial using a commercial device for children with cerebral palsy (ISRCTN17624388; IRAS ethics approval 14 NW 1499). Our study, just completed, explored the potential of utilising a widely available commercial games console (the Nintendo Wii Fit) within the home to deliver regular, tailored physiotherapy schedules of Virtual Reality Therapy (VRT) for children with cerebral palsy in comparison to free play usage. Participating families completed an online questionnaire regarding children's current use of computer games such as Nintendo Wii Fit within the home. They were then randomised into either a supported or unsupported (control) participant group. Supported participants followed a therapist prescribed schedule over a 12-week period, utilising only specified Nintendo Wii Fit games for designated amounts of time per session. Sessions lasted 30 minutes, undertaken three times a week with games selected for specific physiotherapy purposes, such as core stability or balance. During this 12-week period, bi-weekly telephone contact to families oversaw the child's progress, updated game selection and responded to any queries. Parent, carers, and children were required to keep a simple daily diary to rate sessions. Unsupported (control) participants used the Nintendo Wii Fit for 30-minute sessions, 3 times a week, over a 12-week period. However, they had a free choice over which games they chose and the duration of each game played within the session. Bi-weekly phone contact was also made during the 12-week period. Parents and children were also requested to keep a simple daily diary to rate sessions. Assessments of balance and functional mobility were taken at three time-points: before commencing the trial, halfway through, and on completion. An exit questionnaire asked parents and children to report on factors such as engagement, ease of use and fatigue.

In each section of this article we return to our study to provide grounded examples. First we discuss our study as a context for where the placebo effect fits into complex interventions incorporating digital technology. Second, we discuss placebo, its history and use in clinical trials is discussed. Placebo constraints are made up of four factors: a) the placebo effect, b) the placebo delivery c) the placebo object, and d) the way in which placebo controlled trials measure output. Last, we give further examples of where the placebo with digital technology has been tried and could have a medical application. There are as yet few examples of this type of intervention trial, but given the potential for growth with digital technology, especially with mobiles, this is set to increase.[3] Our examples show different contexts and types of research incorporating digital technology where placebo effects are tackled or controlled. We conclude by conjecturing as to whether complex interventions using digital technology will enable the appropriate construction of placebos and enable fair comparisons.

A Complex Intervention and Placebo

Complex interventions require careful planning around the practical effectiveness of an intervention, how the intervention exerts its effect and how interactions between components change across intervention groups.[6] An effective intervention that produces meaningful outcomes may change completely if there is additional impact of technology on placebo.

For our study, a traditional control group of "best pre-existing current treatment" (most likely standard physiotherapy) therefore was considered a difficult option due to the current lack of understanding of a placebo effect with technology.[4] For example, other factors e.g. the Hawthorne effect or observational bias may occur as a result of simply being watched during an intervention. The actual impact of using digital technology is not as yet known, comparing a virtual reality group with a group without virtual reality is an option but could have overstated benefits. A comparison group considered children standing on a wobble board, whilst watching a video of the sports/activities that would be played on the gaming system on a large screen. This option was close to the digital version, but was comparing a digital with a non-digital version.

However it was decided that both groups would have to be given the digital technology but with subtle differences between groups, as there was no way to control for hidden effects of the digital technology. Group 'A' became a supported therapy group, with a prescribed programme of therapeutically oriented games for targeted skeletal-muscle groups, a suggested number of times per week for activity, and bi-weekly phone calls by a physiotherapist. Group 'B' became an unsupported group with un-prescribed access to the console, with suggested number of times per week for activity on the console, and bi-weekly phone calls from research staff to see how the

participants were progressing, but without offering structured or scaffolded learning support.

Our choices regarding trial groups were altered because of the possibility of hidden and unforeseen effects of technology that led us to ask: What constitutes placebo? What are the wider implications for placebo with complex interventions when digital technology is incorporated? What implications does this have on fair comparison in complex interventions? We now address these questions by looking at the constituent parts of the placebo effect, its delivery, the object that is the focus of the placebo, and how hidden effects get measured or are controlled.

What is a placebo?

A placebo is often used to find out whether a treatment has real or just perceived benefits. Placebo has been shown to be in some cases as powerful as an active intervention or drug and "conveys meaning, influences expectations and possibly triggers conditioned responses or behaviour changes"[11], so that "[t]he simple act of receiving any treatment (active or not) may in itself, be efficacious because of expectation of benefit".[10,12] This meaning has gradually been extended to include receiving, or simply seeking medical attention, and can sometimes be enough to help patients recover.[13]

Doctors have often realised that illness can be self-limiting, and so may give an inactive treatment, with the outcome being that a patient might benefit psychologically. Medically the term has been in use from as early as 1772, with the term entering the medical lexicon increasingly in the 19th century.

Placebo can account for as much as 30-40% of patient relief for ailments such as pain, blood pressure, asthma, and coughs.[14] What is unclear is how placebo actually works. Factors as strange as drug packaging can impact on effectiveness.[4] The placebo effect is a conglomeration of effects rather than any single entity. Brissonnet[15], suggests that literature on the subject of placebo prior to 1996 may even be faulty, as our understanding of placebo was incomplete, and whilst Brissonet is concerned with medical placebo the observation is appropriate given the subsequent growth of mobile and digital technology. Yet, the significance of placebo is such that Curie et al (2015) report that even for individuals with an intellectual disability they are still effective, warning of dangers "when testing novel treatments" due to contextual factors.[31] Curie et al also suggest limits to the impact of placebo as individuals with co-morbid dementia showed no placebo response, whilst the higher an intelligence quotient score the greater the likelihood of response.

For our Virtual Reality feasibility study, the simple act of using a commercial console by children may well have been enough to obtain functional improvement but this is further complicated by benefits of the therapeutic programme or natural development with age. Further, if individuals and families are biased toward the benefits of digital technology or mobile smartphone use, this may change attitudes, opinions, perceptions, and outcomes with technological intervention, even if there is no actual benefit. The use of digital technology makes it difficult to identify those causal factors that can cause positive change.

Placebo is an umbrella term

Placebo in healthcare evaluations is complex, and can be thought to comprise three key elements: the effect, the delivery and the object.

1) The Placebo *Effect*.

Placebo effects occur because of the feeling or perception that an intervention is working and has associated wellbeing, which is produced by the placebo, pure or pseudo.[15] Homeopathic treatments are a good example of pure placebo, as described in Ben Goldacre's book *Bad Science*[4], as the chemicals are on the whole dummy treatments. A placebo effect is problematic however, as a lack of active ingredient somehow causes physical change.[16] Placebo is inert, so the placebo *effect* is also rather referred to as a meaning response.[16] For example, studies where there is an effect of the placebo such as blue pills being judged as depressants, and red pills being seen as dangerous, subsequently participants experience exactly that - a blue pill depressing a participant, a red pill judged as danger, it is highly likely that the same effects may occur with company names, or the colour of mobile phones.[16] Meaning response permeates all interactions between clinician and patient, such as manner, language, dress, diagnosis, and prognosis.[16] Therefore, 'placebo effect' refers to the meaning response from the participant that is desirable and is under investigation. Meaning response that is undesirable and not under investigation is now commonly referred to as the "nocebo effect".[17] For example, inert treatments

not under investigation and that produce endogenous opiates in participants would be nocebo.[16]

Complex interventions that incorporate digital technology may result in a potential meaning response with associated wellbeing. For example, the simple presence of a commercial console (e.g. Wii Fit) may change beliefs and attitudes about its effectiveness as a therapeutic device, producing a desired outcome based on feelings or perceptions that the technology is going to have an effect. But it would be vital to know what element of meaning response is under investigation, especially when the active elements of digital technology are still unclear.

2) The Placebo *Delivery*.

If placebo effect is constructed from wanted and unwanted meaning response constructed through interaction, how placebo is given or delivered to the participant or patient is also important. This is the who, where, and when of the placebo, and not only includes the meaning response generated by the doctor or health professional, but also includes the context in which the placebo is given, the immediate timing of the placebo, and the perception of interventions over time. Context effects and impacts in medicine, so-called 'optimal healing environments' are well researched, and include factors such as expectations to treatment and empathy.[11,16] For example, delivery tends to work better if a drug is subcutaneously injected as opposed to taken orally, it is also better if given with empathy rather than neutral manner.[11,18] Placebo effects are also larger when the mode of delivery is physical (see the placebo object below), as opposed to pharmacological or psychological.[19] Placebo delivery with digital technology is as much to do with rituals, or activities that routinely occur in a set order, as well as ideas surrounding computers and mobile technology during interaction that surrounds patient consultation.[13] Delivery is not limited to a clinical setting, as seen by advances in tele-health care, as mobile delivered interventions are more likely to occur in the home, which may or may be not be considered an optimal healing environment for complex interventions incorporating digital technology. The place, timing, and delivery of therapy with a commercial console or piece of equipment for example will therefore further complicate the impact of technology. Recent evidence on the impact of mobile phone screens on melatonin and sleep levels shows how physical response is genuinely affected, linking the bluer end of the light spectrum used in screen devices to common alert states of behavior.[33,34] In our study we were using the commercial console in the home. Use in the home may change the clinical effect of the console, as the clinical relationship of patient-health professional has been removed, as has the time of day when the technology may be used, creating further possible positive or negative effects.

3) The Placebo *Object*.

Placebo effect is the 'meaning response' (see section 1 above) under investigation; the delivery is the manner in which the agent causing change is transferred to the participant. The placebo object is the focus of the intervention i.e. the drug, therapeutic intervention (e.g. needle in acupuncture), packaging, smartphone, or machine that might be used in a clinical trial. This overlaps somewhat with the meaning response but focuses on the physicality of an object, referring to the attributes and expectations given to a particular object. The object at the heart of the intervention can be vested with a wide variety of meaning response, from a needle – potentially negative – to positive such as the colour of packaging on a headache or smartphone tablet box implying cleanliness, purity or relief from symptoms. The physical object that is the focus of the placebo may well alter with the type of digital technology. If a placebo *object* is a computer or mobile phone, then the type, (e.g. familiar, novel, bespoke, 'off-the-shelf', old) of computer becomes important. Computers such as a desktop, a smartphone, a tablet, a Radio Frequency Identification (RFID) tag, or a smart-object all change the dynamics of interaction. If a patient-clinician relationship alone improves outcomes[13], a patient-object (e.g. the computer) relationship may also improve or worsen outcomes similar to how tools like stethoscopes are considered an important part of clinical rituals.[13] The object, when presented in the right clinical way, vested with important attributes such as validated tests, becomes imbibed with clinical meaning.[20–22] For digital technology such as smartphones, the value of placebo as an object, exposes the importance of what Gibson called object affordance, or the perceptual cues and clues that imply how the object will be used.[22] For our feasibility study it may be that positive outcomes could be explained away simply because we made the console the subject of a health study.

Once the placebo is delivered through an object like a smartphone we have then selection of criteria applicable to establish a placebo:

1. Placebo effect or meaning response i.e. the *feelings and perceptions that individuals have* of the placebo/intervention
2. Placebo delivery: The *interaction that occurs during the delivery* of the placebo/intervention
3. The physical object itself e.g. the mobile element such as a smart phone

All three need careful consideration if mobile technology delivers a medical intervention. It may be prudent to survey participant's attitudes and perceptions toward mobile technology itself prior to data collection, or have attitudes specified as complicating factors in analysis plans. Internet and mobile addiction could for example confound results if as recently found, individuals who have lower working memory capacity and poorer attentional control are more prone to problematic mobile phone use, and are less resilient to digital media distraction.[23] The type of mobile e.g. branding, aesthetic factors may also need to be carefully planned. How the intervention is delivered will also matter, for example whether the intervention is to be delivered via software at home or whilst at a clinic.

There is however, further complication when considering placebo use, and that is how placebo effects are measured.

The Placebo Effect measured

This is the output caused by the apparent action of the placebo. This is greatly complicated by factors that can influence measurement. The placebo effect is often confused with other confounding factors in experiments.[15] Measured outcomes as a result of a placebo trial may in fact be due to a multiplicity of unintended factors.

For example, the *Hawthorne* or *observer effect* occurs where individuals change their behaviour simply because they believe they are being observed.[29] A positive interpretation by participants of the Hawthorne effect is known as the *Demand effect*; participants think they know what experimenters are looking for.[29] If participants are presented with information differently, e.g. positive or negative delivery by an individual, this becomes the *Halo Effect*.[18] Where an intervention is out of the ordinary, an occurrence that is common in the mobile and digital technology field, behavior may change simply because of the *Novelty effect*. The *Will Rogers phenomenon* occurs where changes in diagnostic criteria seemingly produce improvements in prognosis for individuals, especially when diagnosis improves early detection and so patients appear to live longer. *Simpson's Paradox* occurs where trends in experimental findings can be completely changed if sub-groups are analyzed separately or together, such as trends in data can also completely disappear.

What we can see is that not only do treatment or intervention protocols need to be carefully designed, but that with the introduction of digital technology additional confounders of attitudes, objects and delivery potentially require further planning before trials get underway.

Placebo in Complex Interventions Using Digital Technology

Traditional placebo effects are based on an individual ingesting a drug, or taking part in an intervention that is believed to be effective as a treatment. For example, the participant agrees that they may be getting absolutely nothing within a clinical trial, but they may be willing to take that risk (e.g. new phone based method of delivering cognitive behavioural therapy) if the risks are offset by increased life expectancy. However, if hidden factors surrounds a digital object e.g. through a screen, a monitor or a mobile, this makes placebo additionally complex, and may not carry the same weight in terms of life and death decisions. For example, the 'on' and 'off'-ness of digital technology is problematic; dummy technology cannot be 'on', deliver therapeutic *effects,* and deliver bogus therapy at the same time. Some research has attempted to do exactly that, replicate digital technology, yet give dummy feedback to the participant.

Heywood and Beale[24] used EEG to look at the difference between the delivery of a biofeedback tool for children with Attention Deficit/Hyperactivity disorder (ADHD). In the experimental condition children with ADHD were given a standard EEG biofeedback treatment that reflected their affective state, designed to alter behaviours synonymous with ADHD. This was alternated with a placebo protocol identical to the treatment but with averaged EEG feedback from all participants and so not linked to the individual's real affective state, with

the hypothesis that having real-time information would enable individuals to recognize when they were becoming hyperactive, or likely to lose interest. The result was that the live EEG feedback produced no difference to the placebo compared to baseline levels and as a result reinforces the need to test out the salient ingredients of any given intervention when using digital technology. However, as is discussed below, the use of a placebo without a control condition lessens the power of findings.

Chittaro and Sioni[25] developed a game that detects a user's level of stress and depression and then feeds that back to the individual in the form of a 3D virtual character which embodies the state of the person, with the aim of influencing the person's affective state. In their placebo condition the user's stress level was measured by pseudo-randomly taking into account real time readings from physiological sensors. The experiment used two further types of sensor, a single physiological sensor, which measured skin conductance, and a second sensor that detected four types of affective information, skin conductance, heart rate, and the muscular response of two muscle receptors. Their findings showed that only the single physiological sensor was better than the placebo condition, therefore the placebo was the same as the multiple sensor in allowing individuals to alter their affective state based on biofeedback. In both of these experiments the use of a placebo condition, or a dummy treatment showed that digital treatment was not effective.

Some work within tangible computing, and the 'internet of things'[26], a branch of computer science that uses digital tags embedded within objects, has attempted to use a control condition not as treatment as usual, but as an experimental condition but with digital technology simply turned off. Obviously for screen-based digital technologies e.g. mobile, tablet, multi-touch surfaces, technology being off is problematic, however for technology that is within the 'internet of things' this may have less impact. In a number of novel experiments Hinske et al[27,28] looked at a child's play environment which was augmented with RFID antennae and Dolby stereo. In these experiments a toy, a Playmobil knight's castle was either used with digital augmentation turned on or off. Both play environments were therefore valid as they were using the same object, but with only one augmented with digital feedback. When comparing children's play with the augmented knight's castle and with the knight's castle, it was found that the augmentation promoted more talking and more interaction. In the augmented knight's castle there is a problem if a placebo condition was tried in that there is no way the technology could deliver the same effects experienced with the digital technology in a bogus way, as children's activity with toys caused digital feedback to occur. In this instance, activity dependent differences in digital feedback confounded comparison between placebo and real conditions.

More recently, Denisova and Cairns (2015)[33] have shown that a placebo effect can occur in digital games when users are primed to expect certain features of a game, which in due course resulted in deeper immersion. When users thought artificial intelligence was switched on during game use, even though it was not, deeper immersion was reported.

In certain circumstances it is impossible to construct a placebo using digital technology because the technology is either on or off. Further, placebos with digital technology are currently never ingested, invasive, or part of the human body. A true digital placebo might begin to have a place in experimentation when digital tags are placed under the skin of workers. This could be used in clinical settings with slow-release drugs, controlled by digital technology, or to investigate further the patient-clinician relationship if clinicians were tagged and then factors affecting measurement such as the Hawthorne effect were purposefully manipulated. The placebo object may be useful if wearable technology is being used to gather data about user head motion or stability, eye gaze, gross motor function, especially if it is impossible to tell if the technology is switched on or not.

Conclusions

Whilst medicine still debates the impact of placebo, it appears that there is a multi-faceted definition of what constitutes placebo. Further, investigation into cumulative effects of individuals receiving placebos over time does not as yet show effective ways of estimating the effect of placebo.[11] Whilst the best use of placebo employs RCT double blind methodology (e.g. BOTXN versus saline injections) with a no-treatment control group, even this complicates methodology by introducing a third group.[11] There is as yet mixed evidence for the placebo effects in clinical trials, but evidence is growing for placebo interventions being now statistically (but not necessarily clinically) significant for "patient and observer-reported continuous outcomes".[19]

A placebo paradigm using digital technology may only be useful in healthcare settings only if all sub-factors are taken into consideration; the feelings and perceptions of individuals, the measurements being taken, the participant group, the interaction and delivery of the placebo and the placebo object itself. Mobile technology in medicine is bound to bring with it a new type of meaning response, which will require careful adjustment to counterbalance effects. Surveying a population may be one way to begin to understand hidden factors if a study is at risk, prior biases could therefore be carefully considered before beginning a trial. Checking the acceptability of a new intervention through patient and public involvement before trial may also reveal any hidden effects that may occur. The uses of new methods of data capture e.g. mini-RCTs[35] where participants may be in more than one experimental group depending on activity, offers novel ways of accounting for individual variance. It is conceivable that groups could and should be constructed within a trial based on prior average daily smartphone use, age, demographics, or whether their preferred mode of delivery is tablet over smartphone. Ultimately the impact of hidden effects of digital technology will come down to the efficacy, method and planning of the trial, and as long as software, human computer interaction experts, and clinical teams work together closely the "more hype than hope"[36] accusation aimed at digital technology should not arise.

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