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Investigating placebo mechanisms: could a PDP system exist?

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Abstract

Placebo mechanisms are a neglected area of research. Kirsch's (1985) response expectancy theory described the stimulus-placebo response process as direct and unmediated. However, Hyland (2011) argued that the placebo effect is mediated by a parallel distributed processing (PDP) system, whereby all cognitive input is processed simultaneously, resulting in perseveration of the placebo effect. The present study examined this theory by utilising a TENS device as a placebo 'effecting' reaction times to a computer task, with an additional cognitive load task to further test the PDP system's existence. Although a general placebo effect was found that increased in the cognitive load conditions, no evidence of a perseveration effect was obtained. Possible reasons for this and implications for future work are discussed

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Introduction

With increased amounts of research being dedicated to uncovering the possible mechanisms through which placebos exert their influence, it is important to acknowledge the views put forward by theorists regarding the possible mediating processes between stimulus and placebo response. In essence, the placebo effect is the psychological or physiological response to an inert substance or procedure (Stewart-Williams & Podd, 2004). There has been much dispute as to the underlying mechanisms that cause it, but wide agreement that it transcends personality, gender, and culture, and is not limited to the type of treatment used (Geers et al., 2005). As research continues to show, the placebo effect is a genuine phenomenon that can affect everyone and has the potential to improve the body's physical symptoms without real medical intervention.

There have been several attempts to explain the placebo effect in terms of its principal underlying mechanism, with aspects such as cognitive anticipation (Tolman, 1932) and emotional change (Brody & Brody, 2000) being highly regarded (Geers et al., 2005). The two main models of the placebo effect are expectancy theory and the classical conditioning approach. Expectancy theorists maintain that the placebo effect is a response to a placebo treatment which is driven by the anticipation of a particular outcome (Stewart-Williams, 2004). On the other hand, those who have adopted the classical conditioning approach argue that the placebo effect is a consciously or unconsciously learned response to a stimulus. It has been applied it to the classical conditioning paradigm first described by Pavlov (1927), whereby the repeated pairing of an active substance and a placebo over the course of a medical treatment will result in the placebo becoming capable of eliciting a response similar to that of the active substance (Ader, 1997). These models are often pitted against each other because they outline different processes that mediate the placebo effect. However, as it will be shown, perhaps these two interpretations of the placebo effect are not mutually exclusive (Kirsch, 2004), and have paved the way towards a sophisticated neurological-based explanation of the dynamic mediating process between stimulus and placebo response, examined through compliance to suggestions once they are known to be false (Hyland et al., 2011).

As mentioned previously, the conditioning approach outlines that the placebo effect can be achieved when a substance or therapeutic procedure is associated, either consciously or unconsciously, with a specific effect, causing it to become an agent for this outcome (Bensing & Verheul, 2010). Voudouris et al. (1985) provides an empirical example of the conditioning mechanism: through a series of conditioning trials, they were able to produce a placebo response to a placebo analgesic cream by manipulating the pain stimulation levels that the participants received. The results confirmed that the placebo response could be conditioned through non-conscious awareness; participants who were subjected to surreptitiously lowered pain intensity reported feeling less pain, contrasting to those who reported feeling more pain when an increase in the pain stimulation was paired with administration of the placebo. In a subsequent study, Voudouris et al. (1990) attempted to replicate these earlier findings, but also examined the role of verbal expectancy in the placebo effect. Results suggested that conditioning was a more powerful means of creating a placebo response than verbal expectancy because the placebo effect occurred within the conditioning manipulation and opposed the expectancy (Pollo et al., 2001). Voudouris et al. (1990) took this to demonstrate the

superiority of the conditioning mechanism over the expectancy model of the placebo effect.

Although this provides support for the view that placebo responses are perhaps unconsciously learned through classical conditioning procedures, others have disputed this finding. Expectancy theorists depict placebo effects as a product of the recipient's anticipation of a specific outcome; a placebo produces an effect purely because the recipient expects it to. Overall, the support for expectancy theory is substantial and consistent, with many robust effects found concerning its mediating effect. Montgomery and Kirsch (1997) replicated the conditioning procedure that Voudouris et al. (1990) had implemented, but in order to test the relationship of expectancy and conditioning in the mediated placebo response, the informed group were aware that the intensity of the stimulus was going to be lowered during the trials. It was found that conscious awareness eliminated the conditioning effects of pairing pain reduction with the analgesic, thereby indicating that the effects of conditioning were entirely mediated by expectancy (Kirsch, 2004).

Furthermore, there is a considerable amount of other research that has demonstrated the consciously mediating role of expectancies through the application of neurocognitive techniques to placebo analgesia; Zubieta et al. (2005) used fMRI imaging techniques to show that the expectation of pain relief via a placebo with expected analgesic properties was capable of moderating physical and emotional states. This was shown to occur through its mediation by the pain-suppressive endogenous opioid system, thus supporting the view that expectancy can directly produce placebo effects.

Despite these two widely accepted theories, others have put forward alternate explanations of the prospective variables involved in the mediation of the placebo effect. Tolman (1932) proposed a cognitive-based explanation of the conditioned-expectancy mechanism; he did not accept that the conditioning process simply established an unconscious link between the stimulus and the response, such as that proposed by Voudouris et al. (1985). Instead, he argued that an organism acquires a cognition allowing it to predict the sequence of events by learning that the conditioned stimulus (active substance or procedure) is a reliable signal for the occurrence of the unconditioned stimulus (placebo), and thus form a preparatory response. This interpretation implies that the organism being conditioned is cognitively active in the process as it anticipates an outcome, suggesting that expectancies can be shaped by conditioning procedures (Stewart-Williams & Podd, 2004).

A second alternative explanation is emotional change theory which states that placebo effects are the product of a change in emotional state; taking a placebo leads to the elimination of undesired symptoms and thus enhances health through anxiety reduction (Brody & Brody, 2000). Although it has been accepted that psychological placebo effects, such as increased hope, are a likely result of some emotional changes in patients (Barlow & Durand, 2009), this theory cannot account for the precise underlying mechanism involved in eliciting a placebo effect. Consequently, it was incorporated into an expectancy-based account whereby, according to Stewart-Williams (2004), emotional change is the possible mediating variable between expectancies and response.

Therefore, conditioning and expectancy are perhaps not mutually exclusive processes; conditioning procedures produce an association between the stimulus and a

representation of the outcome - an expectancy. Conceivably, this suggests that conditioning is not so much an automatic process which evades cognition, but is actually a component of expectancy (Kirsch, 2004).

The majority of expectancy theorists accept that conditioning procedures are capable of producing placebo responses, which they maintain are *placebo response expectancies*; therefore it is the expectancy that elicits the response. Kirsch (1997) put forward his theory of response expectancies, which he described as "automatic consequences of one's own belief" (Kirsch & Lynn, 1999), including anticipations of one's own automatic, subjective, and behavioural responses to situational cues, which are directly self-confirming (e.g. expecting to feel more alert after drinking coffee).

Kirsch (1985) posited that there are no intervening psychological variables between a response expectancy and the generation of a placebo response. This notion was developed in his immediacy hypothesis, which described it as an unmediated causal relationship between response expectancy and expected response because effects are experienced as automatic. Kirsch and Weixel (1988) demonstrated this through the physiological changes that were observed in individuals' experiences directly after the administration of a placebo; physiological effects were measured after the participants had consumed placebo (decaffeinated) coffee. It was found that deceptive administration of the placebo coffee produced physiological effects that mimicked the consumption of real coffee, such as an increase in pulse rate and increased alertness. However, some of the participants who were aware that they might receive placebo coffee showed opposite physiological effects to those in the deceptive administration condition, suggesting that it is the individual's belief about the effects of a substance or procedure that is imperative to producing a response to a suggestion (Kirsch & Weixel, 1988).

Specifically, Kirsch (1997) proposed in his immediacy hypothesis that there is a unique causal pathway between each response expectancy and response. His reasoning for this stemmed from his belief that some connections among variables had to be unmediated; otherwise there would be an infinite number of intervening variables. Using the example of subjective states, Kirsch (1985) stated that expectations for a subjective state can lead directly to that state and are therefore unmediated. For example, one might feel anxiety from the expectation of anxiety. Kirsch (1985) also applied this to objective states, which he viewed as autonomic responses that are directly connected with subjective states (Stewart-Williams, 2004). For example, one may experience increased heart rate when aroused. An investigation by Koyoma et al. (2005) into the neural mechanisms underlying expectations of pain revealed that the anticipation of an impending stimulus can shape neural processes that occur in the brain; when participants anticipated that a stimulus was going to be painful, there was an immediate increase in the activation of the thalamus and prefrontal cortex, which overlapped with activity in brain regions associated with expectation. This supports Kirsch's belief that response expectancy effects are an automatic and direct process, without any influence from mediating variables.

Despite this research, which has been highly influential with regard to the possible mechanisms that elicit the placebo effect, Hyland (2011) put forward a different account of expectancy and response that opposes Kirsch's (1985) view that placebo effects are the result of an immediate and unmediated process. This account argues that there is in fact a mediating process between the generation of an expectancy and a response; an

automatic system intervenes when an expectancy is generated, and a subsequent response is produced, although the effects are not immediate. Hyland (2011) proposed that this intervening system within the brain is a parallel processing system that consists of interconnected units that relay information by activating or inhibiting connections.

Hyland's theory is based upon a parallel distributed processing (PDP) model of the brain and body as a complimentary entity that attempts to explain information processing in terms of a network of neurons in the brain (Hyland, 1985). As specified by McClelland and Rumelhart (1986), the PDP model has three assumptions: that the representation of information is distributed and not local; that memory and knowledge for specific things are stored in connections between processing units; and that learning can occur gradually through experience due to changes in connection strength. Hyland (2011) acknowledged that a strengthening in connections between the units (neurons) within the network is how information can be distributed throughout it, a process that occurs in parallel, rather than sequential, operations.

In terms of the placebo effect, Hyland (2011) suggested that it is produced when an expectation to a suggestion is made and consciously mediated by the parallel distributed processing system. The underlying assumption is that the mind is massively parallel; it simultaneously processes large amounts of information, which subsequently produces hysteresis (a lagging in the time between cognitive input and response output) (Hyland, 2011). This perspective has been supported by the neuromatrix theory of pain proposed by Melzack (2001), which views the body as a unified cross-modal system that encompasses pain into an array of interconnected neurons. Although this theory is based on the mechanisms that underlie pain rather than placebos, it proffers a view of the body that is similar to the model proposed by Hyland; the neuromatrix permits the parallel processing of sensory inputs that are then distributed throughout many areas of the brain and body, comparable to the parallel processing of information by the brain and body as a unified entity, described by Hyland's (2011) PDP theory.

Hyland (2011) argues that hysteresis demonstrates that a PDP system exists in the brain because the simultaneous processing of information will lead to the perseveration of the placebo response (Hyland et al., 2011). This is due to time differences between the onset of cognitive input, the processing of this information, and the response, implying that response to a placebo stimulus will not be immediate (Hyland et al., 2011), contrary to Kirsch's (1985) perspective. This notion of cognitive perseveration has also been endorsed by Brosschot et al. (2010), who postulated that the slow recovery of an individual after experiencing psychological stressors must be due to more than just biological mechanisms alone; they suggested that a process of 'perseverative cognition' causes the effects of stressors to persevere, and speculated that this is perhaps due to the creation of mental representations of stressors which proceed long after the event has occurred. This is comparable to Hyland's theory because expectancies are viewed as internal representations processed alongside other information by the individual, which subsequently results in the perseveration of a response.

Hyland et al. (2011) tested his hypothesis using a reaction time task, whereby participants were led to believe that a transcutaneous electrical nerve stimulation (TENS) device would have an effect upon their reaction time; some were informed that the electric current emitted from the TENS device would make them respond faster, and the remainder were informed that it would make them respond slower. Participants completed three blocks of 100 reaction time trials, but before the third block, half of the

participants were informed that the TENS device was in fact a placebo and would have no effect on their reaction time; any difference in their reaction times would be due to their belief that it had had an effect. Hyland et al. (2011) found that participants' response times did change after they received information notifying them that it was a sham; however, compliance with the suggestion was maintained for approximately 42 seconds after being informed that it was false. These results led to Hyland et al. (2011) postulating that an automatic system had come into effect, as the sudden change in cognitive input (information that the suggestion was false) had resulted in its processing alongside the reaction time task. This caused prolonged compliance with the suggestion (demonstrated by the sustained placebo response) because although the participants were consciously aware that it was a placebo and was therefore having no real effect, there was a delay in this cognitive processing to affect their physiological response, demonstrating hysteresis.

The aim of the current study was to investigate Hyland's theory that a PDP system exists in the brain; specifically, that there will be automatic compliance with the suggestion once that suggestion is known to be false, demonstrated through the perseveration of the placebo effect. This was determined by replicating Hyland et al.'s (2011) study; a reaction time task was used to measure the perseveration of the placebo effect once it was known that the TENS device had no genuine effect. A TENS device emits a small electrical current used for therapeutic purposes, but in this study it was used as a placebo. The device was chosen as an ethically suitable placebo because it has no known health or safety effects, and is simple to use and control. In addition, it was decided that the device would not be a familiar piece of equipment to the sample of participants tested, thus creating a false suggestion more likely to be accepted by the participants as true in order to mislead them about the TENS device's proposed qualities (i.e. that it will effect reaction time). The current study was therefore a replication of the study by Hyland et al. (2011) in terms of design and material.

However, this study aimed to further examine the existence of a PDP system, using the perseveration of response to a suggestion as a measure of compliance. This was achieved by including a cognitive load task condition alongside the reaction time task. The addition of the cognitive load task into the study was necessary to further investigate the notion of an automatic system with regards to the processing of information; if participants were informed that the TENS device was a placebo *and* had to complete a cognitive load task, this would bear a heavy cognitive burden upon the PDP system, resulting in the simultaneous processing of a large amount of information. Any perseveration would therefore imply that a PDP system exists within the brain.

The cognitive load task that was chosen for the study was based on the task used by Rees et al. (2001); an auditory task whereby participants were required to name aloud the words that have two syllables in a list of words played to them. This was chosen as the most suitable cognitive load task because participants in the current study had to complete an onscreen reaction time task, and so an auditory task seemed most appropriate. In addition, the task was deemed as being of medium-level difficulty; participants were required to ignore one and three syllable words, and only say aloud the two syllable words they heard in a list of 60 words.

As well as this, the current study deviated from the original by using a within-subject control that was omitted by Hyland et al. (2011). Each participant had only one arm attached to the TENS device as a control measure; it was randomised as to whether the

left or right arm would be the 'placebo treated' arm in an attempt to eliminate the confounding effect of the left or right dominant hand during the reaction time task.

The current study therefore hypothesised that there would be an effect of instruction on response times which would be in the direction of the suggestion (either fast or slow). In addition, it was predicted that response times would be slower in participants who undertook the cognitive load task. Secondly, the study hypothesised that the TENS device would induce a placebo effect specifically in the 'placebo-treated' arm, owing to the suggestion given to each participant in the instructions. Thirdly, the study aimed to investigate whether participants in the informed condition would exhibit perseveration of the placebo response (hysteresis). Finally, it was hypothesised that this perseveration would be enhanced in the participants undertaking the cognitive load task, because the parallel processing of the information would result in temporary automatic compliance with the suggestion once it was known to be false, as previously found by Hyland et al. (2011).

Methodology

Participants
For their participation, 81 students (33 males and 48 females) from the stage one and stage two psychology programme at Plymouth University were given 'participation points' as part of a course requirement for a compulsory module in research methods. The mean age of the participants was 19-years-old. Sixty-five were right-handed and the remaining 16 were left-handed. No other demographic information was recorded.

Experimenters
Participants were tested by three 22-year-old females studying psychology at Plymouth University. The experimenters wore smart black clothes during the experiments in order to promote a sense of professionalism, and took it in turns to test participants. The experimenters were given identical instructions on how to use the TENS device correctly.

Materials
Numbered envelopes containing 'scientific' rationale (a diagram of a neuron and false information regarding the electrical current produced by the TENS device) were used to create the suggestion that the TENS device would have an effect on response times (see Appendix 1). One was given to each participant and suggested that the aim of the study was to test whether the electrical current of a TENS device would affect their reaction times to an onscreen computer task. Forty-two participants were informed that the TENS device was going to make one of their arms respond faster, and 39 participants were told that it was going to have a negative effect on their reaction time, making them respond slower. Aside from this, the information on the sheets was identical. Five scientific books and the large box that the TENS device was carried in were put in sight of the participants in order to contribute to the expectation, and further their clinical experience.

A computer programme, PsychoPy, was used to carry out the reaction time task. A bespoke design for this study was created to include specific onscreen messages and instructions (see *Figure 2*). A standard set of onscreen instructions was shown to all participants regarding the reaction time task, and instructions on the cognitive load task were verbally given only to the participants that were required to do it (see Appendix 4). The reaction time task involved the participant responding with either a left (A key) or

right (L key) key press in accordance with the side of the screen a target ('X') appeared. Once the participant responded, their reaction time (measured in milliseconds) and whether they were correct or incorrect (indicated by 'correct!' or 'oops!') showed on the screen for approximately 500ms. Between each reaction time frame and target frame, the participant had to fixate on a central point ('+') on the screen before the next target appeared in order to keep their vision focused (see figure 1 below).

Reaction time frame

Correct!
0.236

Target frame

X

Fixation point

+
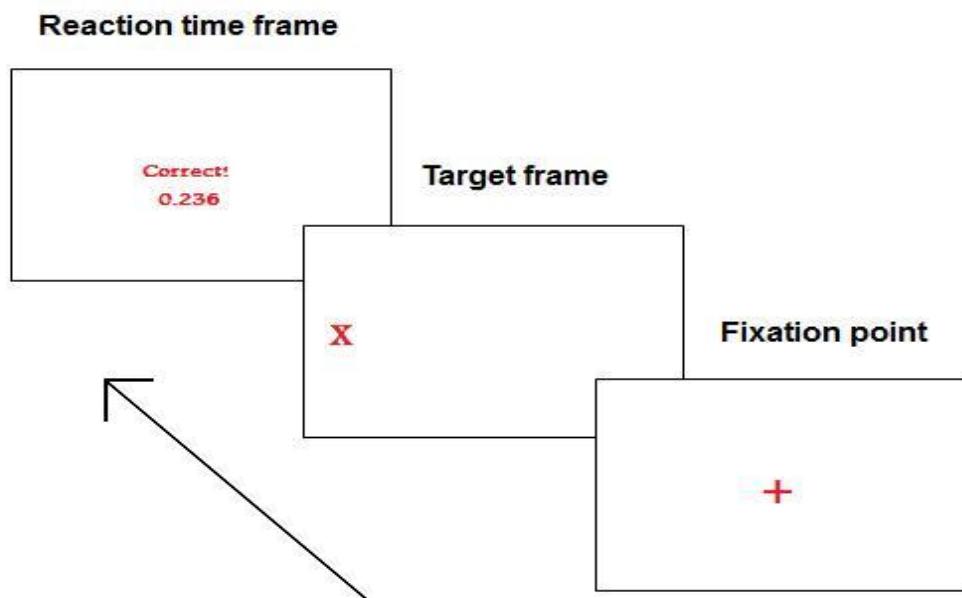
Figure 1: An example of each frame in the onscreen reaction time task experiment.

The cognitive load task was used in four of the conditions and consisted of four audio recordings: one practice trial, which consisted of 14 words and was 42 seconds long, and three lists of 60 words which were approximately two minutes and 22 seconds in length (refer to the attached CD). The recordings were produced by the experimenters using a dictaphone and a list of one, two, and three syllable words (see Appendix 7). These recordings were administered to each participant in a randomised order to eliminate practice effects by using Excel to randomise the order that the three lists would be played. The audio recordings were contained on an MP3 player and were not built into the computer programme. This was to ensure that the experimenter had control over the timing of when each recording was played, rather than having to exit PsychoPy to play it.

Design
A 2 (instructions) x 2 (message) x 2 (cognitive load) between-subjects design was used; each participant was randomly assigned to one of four conditions: informed/fast, informed/slow, placebo/fast, and placebo/slow. This was further divided into two more conditions, whereby half of the participants undertook the cognitive load task and the other half did not (see table 1 below). In addition, a within-subjects control was implemented; each participant produced both a placebo affected score and a placebo unaffected score, which was achieved by having only one of their arms connected to the

TENS device. It was randomised as to which arm (either right or left) each participant was going to have connected up to the TENS device in order to eliminate the effect of 'handedness' on their reaction time scores. This was achieved by assigning each participant number to either left or right using Excel to randomise these factors. The alpha level was set at p<.05.

Throughout the experiments, the experimenters remained blind as to which condition (either fast or slow) each participant was assigned to; this information was contained in envelopes given to each participant. An external person was responsible for the numbering and recording of the conditions each envelope contained. Only one participant was tested at a time to minimise distractions.

Table 1: The eight conditions used in the experiment and how many participants in each condition (n).

	Instructed Fast	Instructed Slow
Informed	Load (n=10)	Load (n=10)
	No Load (n=11)	No Load (n=10)
Not Informed	Load (n=10)	Load (n=9)
	No Load (n=11)	No Load (n=10)

Table one illustrates the eight conditions that the participants were randomly assigned to and how many were in each of the conditions.

Procedure

Upon entering the testing room, the participant was situated in front of a computer screen and provided with a brief outlining the experimental procedure (see Appendix 2), and a consent form informing them of their right to withdraw from the experiment at any time (see Appendix 3 and refer to the attached envelope). They were also informed of these rights verbally by the experimenter. After consenting, they were given a numbered envelope which contained written instructions about the purported aim of the experiment and 'scientific' rationale to make the suggestion more convincing; 42 of the participants were informed that the electric current would make their treated arm respond faster during the reaction time task, and 39 were informed that it would make their treated arm respond slower. Aside from this, all of the instructions were identical.

Verbal instructions were given to the participant by the experimenter regarding the TENS device, and the experimenter then attached the two electrodes from the device to either the participant's right or left forearm. Whereas normally a TENS device is used to stimulate nerves for therapeutic purposes, in this study it was purely used as a placebo. Once attached to the participant's forearm with sticky pads, the device was switched on by the experimenter, and the current adjusted to be sub-threshold (at setting number 5 to give a small and consistent pulsing sensation), and turned back off again.

The participant then received further verbal instructions about the requirements of the task and, once they understood these, they were asked to turn their attention to the computer screen and respond with either a left (A key) or right key press (L key). Before the task began, the experimenter was prompted by the computer programme

to enter the number corresponding to the number on the envelope the participant was given into the box on the screen to ensure that the participant's data would be recorded against the correct condition that they were assigned to. Once this was complete, the participant was asked to put the headphones on.

The participant was then ready for the practice trial. The 39 participants who were assigned to the cognitive load condition received verbal instructions from the experimenter about the task. Once they understood, the experimenter pressed the audio recording to coincide with each trial of the reaction time task. During the practice trial, the participant was presented with 10 practice trials of the reaction time task and the practice cognitive load task recording (if they were assigned to this condition). After the practice trial, the participant was presented with three blocks of 50 reaction time trials:

In block 1 of the trials, the TENS machine remained off for all participants. All of the participants received onscreen instructions informing them of how to respond during the reaction time task, and verbal instructions if they were participating in the cognitive load task. In block 2, the TENS device was switched on by the experimenter when prompted by an onscreen message. The experimenter informed the participant that the TENS device was now on, and to continue when they were ready.

After finishing block 2 and immediately before block 3, participants were informed by an onscreen message that they were about to be shown an 'important message' in the next frame that they needed to read carefully and continue with the experiment once they had understood it. They were told to ask the experimenter any questions they had then and not to ask the experimenter any more once the message had been shown. Twenty of the participants who were in the slow condition and 21 of the participants who were in the fast condition were informed via onscreen instruction that they had been misled about the nature of the TENS device, and that it could have had no possible effect on their reaction times. The other 40 participants who were in the uninformed condition remained deceived throughout the experiment, and received a neutral instruction of equivalent visual length (see Appendix 5). They then completed the final block of trials. A visual representation of the experiment can be seen below in Figure 2.

Upon completion of all three trials, the participant received a full debrief, including details of the real aim of the study and the experimenters' and supervisor's contact details (see Appendix 6). They were thanked for their time, and were asked whether they had any questions. They were informed to contact the experimenters or their supervisor if they had any further questions.
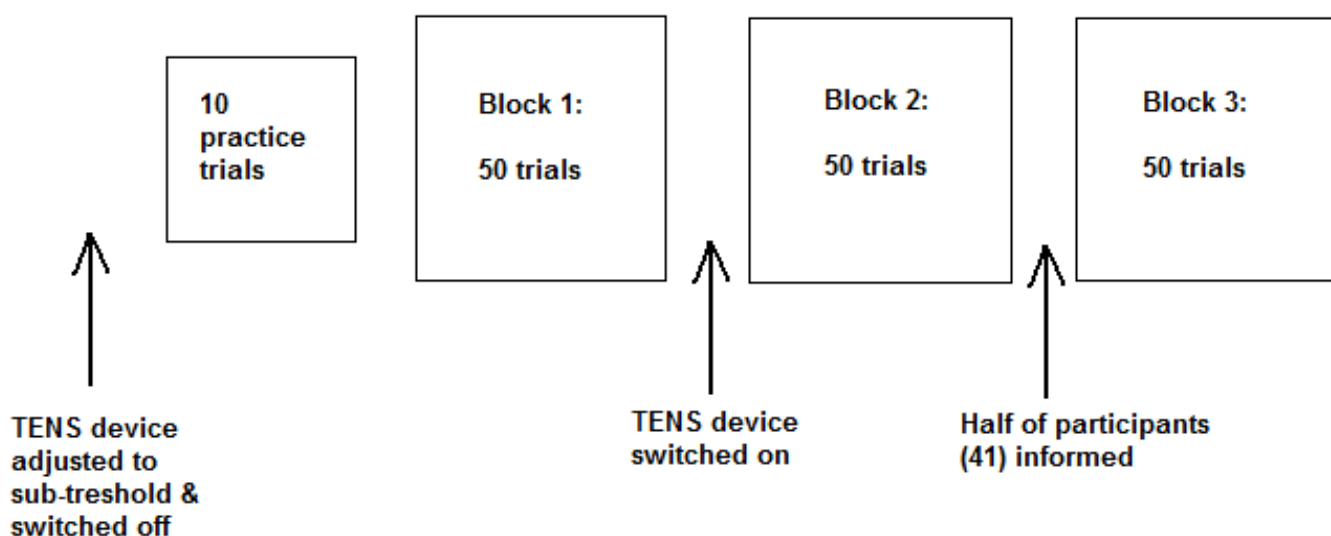
Figure 2: A visual representation of the timings of the experiment

Results

Descriptive statistics for the eight experimental groups are given in Table 1. Raw data is available in Appendix 8 and the attached CD. The hypotheses are answered below.

### Does the load condition slow responses?

An independent samples t-test was conducted to establish whether the cognitive load task slowed participants' response times. The results indicated that the effect of cognitive load on reaction time was as predicted, $t(59.63) = -4.09$, $p > .001$. Specifically, those in the cognitive load condition ($n=39$) had significantly slower reaction times compared to those in the no load condition ($n=42$).

Does the TENS device induce a placebo effect specifically in treated arms?

An analysis of covariance (repeated measures factor: treated/untreated arm; covariate: block 1) was conducted to determine whether the TENS device specifically induced a placebo effect in the treated arm of the participants. Normality and homogeneity of variance could not be assumed, and so the Greenhouse-Geisser correction was used. Results from the analysis of covariance revealed that there was no significant difference between response times for treated and untreated arms, $F(1, 76) = .88$, $p = .35$. It also showed that there was no significant interaction between treated/untreated arm and load (cognitive load/no load), $F(1, 76) = 1$, $p = .32$, or between treated/untreated arm and instruction (fast/slow), $F(1, 76) = .14$, $p=.71$. This is evidenced further by the interaction plot in figure 5 below.

Table 1: Number of participants, mean, and standard deviation of reaction times for the three variables (instruction, message, and load) and the three blocks of trials.

Block	Variable	N	M	SD
	Instruction			
1	Slow	39	354.76	77.24
	Fast	42	352.64	76.2
2	Slow	39	363.83	93.78
	Fast	42	345.48	74.08
3	Slow	39	359.27	86.45
	Fast	42	349.08	82.05
	Message			
1	Not Informed	40	348.09	75.14
	Informed	41	359.12	77.82
2	Not Informed	40	350.28	82.06
	Informed	41	358.05	86.69
3	Not Informed	40	352.29	89
	Informed	41	355.52	79.47
	Load			
1	No Cognitive Load	42	335.9	63.96
	Cognitive Load	39	373.24	84.43
2	No Cognitive Load	42	333.21	60.88
	Cognitive Load	39	377.4	99.57
3	No Cognitive Load	42	336.9	71.93
	Cognitive Load	39	372.71	92.6
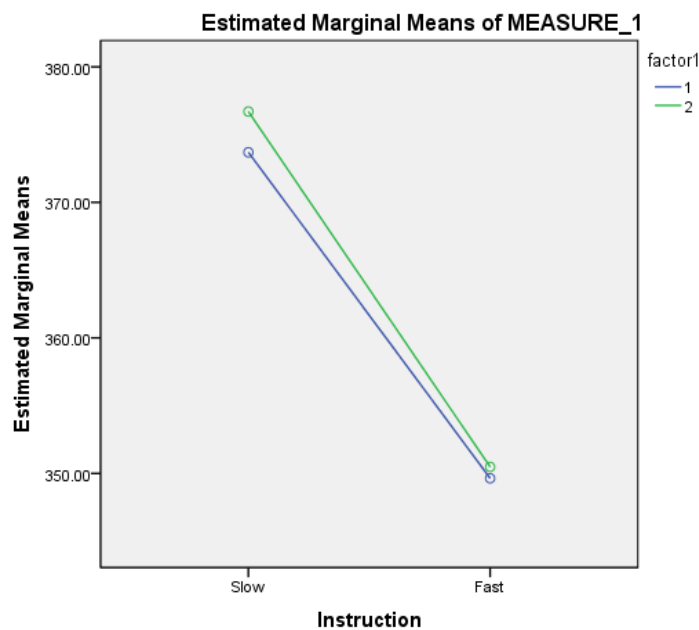
Covariates appearing in the model are evaluated at the following values: BLOCK1RT = 359.8617

Figure 5: Plot of the interaction between treated ('factor1' 1)/untreated hand ('factor1' 2) and instruction (slow/fast)

Figure 5 shows that the placebo effect created by the TENS device was not arm-specific; there was no interaction between reaction times for treated ('factor1' 1)/untreated arms ('factor1' 2) and fast or slow instruction, indicated by the lack of crossover on the plot.

Is there a general effect of placebo instructions on response times?
An analysis of covariance (between-subjects factors: instruction and load; covariate: block 1) was conducted to determine whether the instructions (fast and slow) effected the participants' response times in the reaction time task. Normality and homogeneity of variance could not be assumed, and so the Greenhouse-Geisser correction was used. The results from the analysis of covariance indicated that there was a significant difference in response times between the fast and slow instruction conditions in the cognitive load condition only, $F(1, 76) = .2$, $p<.05$.

In addition, the mean response times for the fast and slow conditions and the cognitive load and no load conditions showed evidence of a speed-accuracy trade-off, and this was inversely correlated; the error rates were higher for participants who had faster reaction times and lower for participants who had responded slower.

Does cognitive load increase or decrease the placebo effect?
The analysis of covariance (between-subjects factor: instruction; covariate: block 1) indicated that the difference between the reaction times in the fast and slow instruction conditions increased in the cognitive load condition only, $F(1, 76) = 12.12$, $p <.001$. This implies that cognitive load increased the placebo effect.
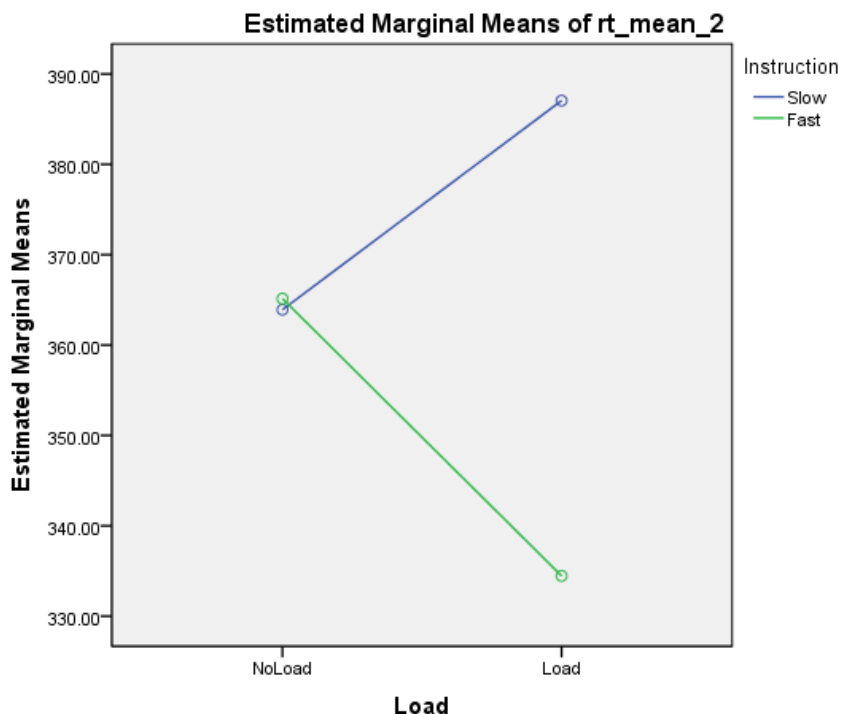
Covariates appearing in the model are evaluated at the following values: rt_mean_1 = 359.8389

Figure 6: Plot showing the interaction between instruction (fast/slow) and the load (cognitive load/no load) condition

Figure 6 indicates that there is an interaction between the load (cognitive load/no cognitive load) and instruction (fast/slow) conditions ($p<.001$). Furthermore, it can be seen that instructions only had an effect in the cognitive load condition, which again signifies that cognitive load increased the placebo effect, thus supporting the hypothesis.

Is there evidence of a perseveration effect?
The independent-samples t-test for the message (informed/not informed) conditions revealed that, with the exception of segment two (trial 11-20), $t(77.33) = 1.99$, $p = .05$, there was no significant perseveration of the placebo effect in any of the other four segments during block three. For example, segment one (trial 1-10), $t(78) = 1.65$, $p = .1$. The results from the independent-samples t-test for the instruction (fast/slow) conditions showed that there was no significant placebo perseveration effect in any of the five segments during block three. For example, segment 1 (trial 1-10), $t(66.63) = 1.6$, $p = .12$. The independent-samples t-test for the load (cognitive load/no cognitive load) conditions indicated that there was a marginally significant perseverative effect in segments one, two, and three within block three: segment one (trial 1-10), $t(62.01) = 2.51$, $p = .02$; segment 2 (trial 11-20), $t(49.83) = 2.01$, $p = .05$; segment 3 (trial 21-30), $t(62.8) = 2.97$, $p = .004$.

Does load increase the perseveration of the placebo effect?
Given that evidence of a substantial and significant placebo perseveration effect was not obtained, it was not possible to test whether or not the cognitive load increased the perseveration of the placebo effect.

Discussion
In terms of the previous research conducted on the existence of a mediating PDP system, the findings of the present study differed in the level of support they provided, with results that were both complementary and contradictory to the hypotheses, and the theory as a whole. A placebo effect was obtained from the suggestions set out in the instructions; however, this was constricted to the cognitive load condition. The perseveration of the placebo effect in block three failed to achieve statistical significance.

The first hypotheses ('does the load condition slow responses?') was proved, as the t-score from the independent-samples t-test was significant, indicating that the cognitive load condition had a negative effect on response times compared to those of participants who did not undergo the cognitive load task. This detrimental effect of the additional cognitive input attained from having a higher cognitive burden was as predicted, and perhaps provides support for the existence of a PDP system; because the participants in the cognitive load condition had a higher amount of cognitive input than those who were not required to do the task, the parallel processing of this additional information perhaps produced slower physiological responses. This interpretation therefore conforms to Hyland's (2011) theory that concurrent processing of cognitive input within the brain causes a slower physiological output (response) by the body.

No significant difference between response times for treated and untreated arms was found by the repeated measures analysis of covariance, disproving the second hypothesis ('does the TENS device induce a placebo effect specifically in treated arms?'). This implies that the suggestions regarding the purported effect of the TENS device upon reaction times set out in the instructions were generalised to both arms in the two instruction conditions (fast and slow). A possible explanation for this in terms of

Hyland's (2011) PDP system theory could be that the expectation of the effect of the TENS device was processed alongside the other cognitive input, such as the reaction time task, and the cognitive load task for the participants in this condition. This parallel processing could then have resulted in the placebo effect becoming generalised to both arms because of the cross-modal mind and body system; the arm that was 'untreated' by the placebo still responded to the suggestion in the same direction that the 'treated' arm did, and was therefore equally effected by the placebo instructions and TENS device. Therefore, this finding can be interpreted in terms of Hyland's (2011) view of the mind and body as a unified entity, and so perhaps provides support for the existence of a PDP system.

The results of the repeated measures analysis of covariance also showed that there was no significant interaction between treated/untreated arm and the load (cognitive load/no load) conditions, or between treated/untreated arm and the instruction (fast/slow) conditions. The most likely reason for this is because of the transcendence of the placebo effect to both arms, and so it could not interact as two separate variables (treated and untreated) with the load and instruction conditions.

The hypothesis that a general effect of placebo instructions would be induced in the participants in terms of their response times was proved ('is there a general effect of placebo instructions on response times?'), as the results of the between-subjects analysis of covariance showed. Specifically, a significant difference in reaction times between the participants in the fast instruction condition and the slow instruction condition was obtained, but revealed that instructions only had an effect in the cognitive load condition. This indicates that the suggestions set out in the instructions, coupled with the utilisation of the TENS device on the participants' arms, caused those in the cognitive load condition to respond in the desired direction.

Firstly, this finding of a general placebo effect provides support for expectancy theory, as well as contributing to this area of research, as it has demonstrated that a specific written expectation, reinforced with the use of a physical placebo, is able to produce specific effects depending on the placebo instructions presented. However, the significant difference between instructions was only found when the cognitive load condition was added, which contradicts previous placebo research. This finding was therefore unexpected considering that Hyland et al. (2011) found a general placebo effect of instructions and did not incorporate a cognitive load task into their study.

A possible explanation for this outcome in terms of a PDP system is that the participants with higher cognitive input (the suggestion and the cognitive load task) had more to process, and so compliance to the suggestion occurred in conjunction with the cognitive load task because deeper and continuous processing was required to compensate for the extra cognitive burden, thus resulting in a placebo effect. In keeping with a cognitive explanation, an alternative reason for this finding could be that the requirement of the cognitive load task furthered the focus of the participants to the task at hand; their cognitive load was higher than those not in the load condition and so they were less responsive to potential distractions in the environment (e.g. noise, the presence of the experimenters etc.), and thus their concentration was kept on the instructions as well as the cognitive load task. However, these possible accounts for the present findings do not explain the previous findings, and so in order to justify the reasoning for this contradictory result, further testing of the interaction between cognitive load and instructions would be needed. This could be conducted through the inclusion of more conditions for different

levels of cognitive load. For example, rather than just two load conditions, as in the present study (cognitive load task or no cognitive load task), perhaps differing levels of cognitive load could be incorporated, such as low-medium-high, in order to uncover whether a higher cognitive load could produce an effect of instructions upon response times.

In addition, it was found that there was an inversely correlated speed-accuracy trade-off in the instruction and load conditions, meaning that error rates were higher in those participants who were responding faster with a higher cognitive load, and lower for participants with slower reaction times and less cognitive burden. Conceivably, this could be due to the 'difficulty' of each trial, determined by the distance from the fixation point (the centre of the screen) that the stimulus was displayed, and suggests that when the trial was difficult within the fast instruction and cognitive load condition, participants had higher error rates (were less accurate) than those who were in the slow instruction and no cognitive load condition. Again, this perhaps provides support for the PDP view of the brain because the high cognitive load combined with faster reactions is likely to result in a greater number of errors when responding to the reaction time task because the physiological response is compromised owing to the high cognitive input.

The results from the independent-samples t-test revealed that, overall, no significant perseveration of the placebo effect was found from comparing the block three response times of participants across all of the conditions, disproving the hypothesis ('is there evidence of a perseveration effect?'). However, a marginally significant perseveration effect was found within the message conditions (informed/not informed) in segment two (trials 11-20), suggesting that compliance to the suggestion once it was known to be false occurred 15-30 seconds into the final block of trials, and then this effect dissipated. This finding contrasts with the previous research, which found evidence of a robust perseveration effect from the beginning of block three for approximately 42 seconds in participants who were informed that the TENS device would not have in fact made a difference to their reaction times (Hyland et al., 2011). Despite the small significance in segment two for the two message conditions (informed/not informed), it is not sufficient enough to be able to state with confidence that a placebo perseveration effect was obtained. Therefore, the final hypothesis ('does load increase the perseveration of the placebo effect?') could also not be tested. Given that a lack of interaction was found between the load and instruction conditions, this outcome was expected; although it was hypothesised that those in the cognitive load condition would show a stronger perseveration effect than those in the no cognitive load condition, the findings above indicated that this could not be possible because instruction only had an effect in the cognitive load condition. Therefore, those participants who did not show an effect of instruction would not be able to show a placebo perseveration effect. It was therefore not possible to test whether the cognitive load task increased the placebo perseveration effect in participants. Owing to this lack of convincing evidence of the existence of a PDP system, Hyland's (2011) theory could not be accepted in this study.

There are several limitations with the study that could perhaps explain why some of the hypotheses could not be accepted. Firstly, the sample was taken from undergraduate psychology students within the university who participated in exchange for compulsory module points. This limited sample makes results difficult to generalise to other individuals, as it is possible that psychology students may respond differently in experiments than others because of their subject knowledge; owing to their participation in other studies, they may have tried to guess the true purpose of the experiment and

either conformed or rebelled against what they believed the aim was, which may have altered their responses. In order to obtain more valid and generalisable findings, a wider and more representative sample of participants would be required, perhaps by encouraging students from other courses to participate and advertising outside of the university to the general public in order to achieve more generalisable results.

The methodology that the study utilised can also be heavily critiqued. To begin with, the presence of the experimenters in the room may have affected how the participants responded in the experiment, particularly because the experimenter testing the participant had to sit in close proximity in order to control the TENS device. This may have been off-putting to the participant, and could have caused them to respond differently in the reaction time and cognitive load task (if they were in this condition) than if the experimenter had been absent, compromising the validity of the data. However, this would be difficult to implement in a future study because the experimenter's presence is necessary to turn on the TENS device at the beginning of block two and monitor the settings for the participant's experience. Alternatively, the experimenter's presence may have contributed to the placebo effect by causing the participant to further comply with the suggestion that the TENS device was going to affect their reaction times; the requirement of the experimenter to constantly monitor the TENS device may have subtly suggested that it was a complex piece of equipment and, coupled with the scientific books and the professionalism put forward by the experimenters' smart dress code, may have reinforced the suggestion put forward in the instructions. Therefore, it may be interesting to test whether the experimenters' presence has an effect upon response times. In a future study, an experimenter condition and a no experimenter condition could be used, with the experimenter only coming back into the room to turn the TENS device on when required.

A second major critique of the study was the use of the computer task to measure reaction times, and essentially, the perseveration of the placebo effect. On average, participants took approximately 15 minutes to complete the study (without counting the initial procedure of gaining their consent, and the debrief following the experiment). Although this is not a particularly excessive amount of time, the persistent need to fixate on the computer screen for 150 trials, as well as process the between-trial messages (and particularly the informed message), may have caused their concentration to wane, and fatigue effects on a diminutive level. Consequently, the participants' response times may have been compromised, and this may perhaps explain why a substantial perseveration effect was not found. In order to control for this, perhaps a different means of testing the placebo effect could be utilised in a future study. For example, rather than measuring reaction times to a computer task, a future study could involve the measurement of other physiological responses, such as strength. This could be conducted by using a similar procedure to the present study; a dynamometer could be used to measure hand grip strength (the physiological response), and placebo instructions and the TENS device as the placebos. After several placebo trials of measuring hand grip strength, a number of participants could then be informed of the placebo via a similar message used in the present study: that the TENS device does not have an effect upon a person's strength and so any difference would be due to their belief that it does. Several subsequent trials could then be carried out, with some participants required to do a cognitive load task, to test whether compliance to the suggestion is sustained for a period of time after being informed of the false nature of the instructions. The difference in participants' strength across all of the conditions and within the trials could then be determined in order to examine any perseveration effect. This set

up may be more effective than the current reaction times study, because participants would not be required to continuously focus on a screen and respond, but instead would just need to apply a short amount of grip on the dynamometer for each trial. Another benefit to this procedure is that placebo effect on strength has not previously been tested, and could have significant applications for aspects of health psychology as well as sport psychology, by applying Hyland's (2011) view of the mind and body as a unified system.

In addition, evidence for the PDP system could be obtained in a future study by examining changes in response times at block two, considering this is when participants are aware that the TENS device is switched on. Any gradual changes in response times after this point could therefore evidence the existence of a PDP system because it would support Hyland's (2011) theory that cognitive processing of information (being informed that the TENS device is switched on) does not result in automatic compliance as proposed by Kirsch (1985), which in this case would be an immediate increase or decrease in response times.

A third critique of the study's methodology is the quality of the methods used to induce a placebo effect, namely the placebo instructions and the TENS device. Other aspects were also modified in order to promote a 'scientific' air to the study; scientific books were put on a desk, and the large box that the TENS device was carried in was visible to create the notion that a sophisticated piece of equipment was being used. The experimenters also wore smart black clothes to further convey a sense of professionalism. Although these other aspects combined with the placebo instructions and TENS device led to the achievement of the placebo effect, alternative methods could be employed in a future study to induce a stronger placebo effect. The written placebo instructions, despite containing carefully thought out 'scientific' rationale, could perhaps have been made even more convincing. For example, a short placebo video could have been made and played to all participants at the beginning of the experiment, containing a false authority figure, such as a professor or scientist, describing 'new research' regarding the effect of the TENS device upon reaction times. This may be more convincing than a single sheet of written instructions, particularly because research in persuasion has demonstrated that people have a tendency to believe what is said by individuals in a position of authority (Cialdini, 1993).

In addition, a more sophisticated and imposing physical placebo than a TENS device could be used in a future study, such as ERP equipment. This may induce a more powerful placebo effect in participants because they may be more convinced that it affects reaction times, creating a stronger expectation. Therefore, the deceptive measures used to create an expectation in the present study could be improved for a future study, in order to induce a more powerful placebo effect than was found.

The practical implications of a well-developed theory and reliable research findings are vast. Although the present study failed to find further evidence of the existence of a PDP system, it did not find evidence for Kirsch's (1985) immediacy hypothesis either; response times did not automatically comply with the new information that the initial instructions regarding the TENS device was false, and so this theory could not be accepted either. The findings of the present study did, however, demonstrate that placebo effects can be induced in participants using an expectation paired with a physical placebo, which provides meaningful support for expectancy theory. The study

demonstrated that placebo effects can be produced for response times, extending the majority of previous research to that outside of placebo medical interventions.

Nevertheless, health psychologists and health care professionals are likely to benefit from a broad range of research within the placebo field, and the placebo instructions and the TENS device used in the present study have several implications. Firstly, the specific methodology that was employed could be applied to health by potentially inducing a placebo effect in something other than response times, such as analgesia. Although TENS devices are generally used as a muscle relaxant, the demonstration of the effect of placebo instructions regarding a piece of equipment in the present study opens up further possibilities for their use. In this sense, the TENS device already has analgesic properties, and so pairing this with explicit instructions regarding pain-relief could potentially induce a powerful placebo effect. This could be valuable to doctors and patients by helping to reduce their pain without resorting to higher doses of medication and potential negative side-effects. However, the use of placebo interventions will always be debated within the field because of the question of ethics that surrounds their use; health care professionals may feel uncomfortable deceiving their patients into believing a piece of equipment has a more powerful effect than it actually is likely to have. Instead, an alternative approach may be to induce an expectation in patients but without resorting to false claims, such as providing them with information of the benefits of using a TENS device to relieve pain, and research that demonstrates its effectiveness. According to Hyland (2011), this approach could be even more effective if the doctor or therapist is sensitive to therapist effects, whereby the bond between the doctor/therapist and their patient ('therapeutic alliance') acts as a placebo in itself. The doctor/therapist therefore has the potential to induce a specific expectation regarding the treatment's benefit to the patient, and higher therapeutic alliance has been found to lead to quicker recovery of the patient.

Therefore, the finding that an expectation paired with a physical placebo can induce a placebo effect, as demonstrated in the present study, has important implications for health; it provides support for the undervalued role of placebos in health care settings and, in particular, the application of expectations, such as patient expectations and how these could be shaped by the doctor/therapist to produce a more positive outcome. Despite the failure of the present study to obtain evidence of the hysteresis of response times and the possible effects of a higher cognitive load, the limitations outlined above could perhaps be taken into account allowing for an improved study to be conducted that could bring forward robust evidence of the existence of a PDP system.

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