The Role of the Prefrontal Cortex in Hypnotic and Placebo Analgesia

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Abstract

Background: Prominent theoreticians have referred to hypnosis as a mega placebo (Kirsch, 1997) or "hypnobo" (Raz, 2007) suggesting that hypnosis and placebo are effectively the same phenomenon. However, there is evidence that their mechanisms of action are different (Parris, 2016a) and that whilst placebo effects rely on the prefrontal cortex (PFC; Benedetti, 2010), the role of the PFC in hypnosis and hypnotic suggestibility is inconclusive. **Methods:** Fifty-four participants (27 male) performed tasks known to tap either left (the Stroop Task; Stroop, 1938), right (the Hayling Task; Burgess & Shallice, 1996) or global PFC functions (Fluid IQ; Wechsler, 1939; 2008). Participants then completed the Cold Pressor Test (CPT), a commonly used test for pain-threshold (the time at which pain is first felt) and pain-tolerance (from pain threshold until hand removal), under three counterbalanced conditions: 1) After receiving a hypnotic suggestion for analgesia; 2) After receiving a placebo analgesia (hand cream); 3) After receiving "cleansing" hand cream. **Results:** Placebo analgesia was not effective on pain-tolerance, but did affect pain-threshold and was related to right and global Fluid IQ, which appeared to positively modify the relationship between the Hayling Task predictor, the right prefrontal cortex and placebo analgesic. Hypnotic analgesia was effective for both pain-threshold and pain-tolerance but was not related to performance on any PFC task. **Conclusions:** The findings showed that hypnotic analgesia was greater in magnitude than placebo analgesia. Additionally, placebo analgesia but not hypnotic analgesia was related to PFC function, indicating that participants with frontal atrophy through stroke or dementia would benefit from hypnotic analgesia but not from placebo analgesia. The results are discussed in terms of both cognitive and neural theories of hypnosis and placebo.

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Table: Figures and Tables

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Thesis Declaration

This Thesis is based on my own work, except for the data collection which was jointly conducted with Anthi Andreou. I helped design the study, I purchased and prepared the apparatus and materials and produced the compulsory forms required for the participants. I also managed the data collection process.

1. Introduction

1.1 Suggestion and the Prefrontal Cortex

Suggestion has been defined as a type of communicable belief or ideation that can profoundly alter an individual's behaviours, thoughts, mood and perception, once the belief or idea has been accepted (Halligan & Oakly, 2014). The phenomenon of suggestion is associated with many forms of human behaviour and as such, growing research has attempted to understand its psychological properties, although it has been argued that the similarities and difference between the many forms of suggestion need further elucidating (Halligan & Oakly, 2014).

Suggestion has also been associated with the frontal lobes of the brain, the area within the brain that is responsible for executive functions (EF) and thus the control of behaviour (Chan, Shum, Toupoulou & Chen, 2008). "Executive functions" is an umbrella term for cognitive competencies which include, amongst other components, the ability to sustain attention, multi-tasking, problem-solving, dealing with novel stimuli, resistance to interference and error suppression. EFs are thought to be housed in the Prefrontal Cortex (PFC; See figure 1 and 2 on page 13), which is the anterior portion of the frontal lobes beyond the motor areas, and which has a putative role in the control of behaviour and thought (Burgess, Veitch, de lacy Costello & Shallice, 2000; Miller & Cohen, 2001).

However, damage to the PFC can change an individual's level of suggestion; for example, Damasio (1994) demonstrated that damage to patients' PFC resulted in them becoming more open to suggestion and vulnerable to dishonest characters and "snake-oil" salesman. Indeed, Asp et al. (2010) demonstrated that patients with ventromedial PFC damage were more vulnerable to believing misleading advertisements, while Cohen & Faulkner (1989) found that atrophy of the PFC in older individuals (a process of normal aging) left them more open to suggestion. Additionally, Ceci, Ross and Toglia (1987) and Bruck and Ceci (1995) found that children were also very vulnerable to suggestion as a process of development, due to the prefrontal cortices taking time to develop in childhood.

The PFC and suggestion have also been associated with both placebo effects and hypnosis, and researchers have drawn links between the two forms of suggestion. However, the reliance of both placebo and hypnosis on PFC function might indicate a dissociation between the two.

1.2 Placebo and Suggestion

A placebo is an inert substance or treatment often presented, for example, in the form of an inactive pill or cream (Zubieta et al., 2005). It has been demonstrated that placebos are influenced by expectation through response suggestion (Kirsch, 1999; Halligan & Oakley, 2014). When told by a physician that a treatment (a placebo) will alter a patient's symptoms positively, the patient will expect that the treatment will work (Hunter, 2007; Kamody et al., 2011; Gold and Litcheberg, 2014). Due to the patient's expectation (an individual's interpretations to suggestions along with their attitudes and beliefs) of what they have been told the treatment can do, their symptoms are then often reduced (Kirsch, 1999), despite the lack of an active ingredient that could be responsible for such a reduction in symptoms (Kamody et al., 2011); this is known as the placebo effect. Thus, a person's expectation can be shaped by what they believe they will experience from a particular substance, rather than by the actual pharmaceutical properties of that substance (Brown, 2015). It has been proposed that expectancies associated with placebo are triggered by social, conditioned, and verbal cues brought on by learned responses, which are then responsible for mediating the placebo effect, through the central nervous system (Colloca & Miller, 2011a; Peirce, 1940). Research has shown within pain studies, that when a patient or participant is given a placebo to reduce pain (the resulting pain reduction is called placebo analgesia), individuals report that their pain has been reduced (Zubieta et al., 2005). In fact, the placebo phenomenon is so powerful that the body's natural painkillers, endogenous opiates, have been found to be stimulated and released in the presence of a placebo (Zubieta et al., 2005). Consequently, understanding the mechanisms of the placebo effect is of great importance. Not only is it important in medical treatment (Kessner, Sprenger, Wrobel, Wiech & Bingel, 2013; Kaptchuck & Miller, 2015), the placebo effect is also important within clinical trials, as it is often used as a control

condition within experimental research to test the effectiveness of new drugs (Kamody et al., 2011; Parris, 2016; Rash & Campbell, 2014).

1.3 Hypnosis and Suggestion

The role of expectation and suggestion within placebo has also been demonstrated to occur within the phenomena of hypnosis (Kirsch, 1999), alongside the use of mental imagery, where it has contributed heavily to levels of hypnotic responding within highly hypnotisable individuals (HHIs), to powerfully change cognitive and perceptual processes (Pearson, Naselaris, Holmes, & Kosslyn, 2015). Like placebo, hypnotic suggestion has also been found to be an effective analgesia (called hypnotic analgesia), within pain studies (e.g. Casiglia et al., 2007; McGlashan et al., 1969; Milling, Kirsch, Allen & Reutenauer, 2005). Unlike placebo, however, hypnosis involves a procedure that typically begins with an induction designed to direct an individual towards a heightened response to suggestion, and mental absorption (Elkins, Barabasz, Council, & Spiegel, 2015). The suggestibility of hypnosis appears to work through the individual focusing on the hypnotist's voice and giving over control of their thoughts and actions to the suggestions of the hypnotist (Parris 2016b). Certain participants (HHIs) are able to experience suggestions more strongly and are more successful at giving their form of control over to the hypnotist, than those lower in hypnotisability (LHIs) (Parris, 2016b). In hypnotic induction, the individual is guided to release thoughts of everyday concerns and focus their attention and concentration on the hypnotist's voice, who gives instructions and directed activities (Landry et al., 2017).

After induction, through the hypnotist's suggestions, there appears a change in the individual's observable behaviours. Changes can include responses to *Ideomotor suggestions* (where the hypnotist suggests that the individual raise their arm in the air, called arm levitation). Also, *Challenge suggestions* (where the hypnotist tells the individual that they cannot bend their arm, called arm rigidity, which is typically an easy form of voluntary action/control). Additionally, *Cognitive suggestions* (cognitive or perceptual distortions, where the hypnotist suggests to the individual that they will not remember undertaking an action, known as hypnotic amnesia). Also, hypnotic amnesia, which includes hypnotic hallucinations (hearing a voice, seeing an object or feeling a sensation that is not real), and hypnotic analgesia, where the hypnotic

response can lead to experiencing pain reduction (Kirsch, 1991). HHIs have subjectively reported that during hypnotic tasks, their mental sets (a subconscious approach to deal with a problem) felt effortless and involuntary, as opposed to conscious and instrumental in effort (volitional mental set) (Tellegen, 1981; Landry et al., 2017). Individuals have also commonly reported behavioural changes such as an enhanced sense of self, relaxation, mental imagery, and changes in perceptions of time etc. (Terhune & Cardeña, 2010; 2016).

1.4 The Phenomena of Hypnosis and Placebo; Similarities and Differences

Placebos and hypnosis involve suggestion. Kirsch (1997) suggested that placebo and hypnosis are a related phenomenon and referred to hypnosis as a 'mega placebo', as hypnosis does not require the deception that placebo requires (Kirsch, 1997; 1999; Kirsch & Lynn, 1995). In a similar vein, Raz (2007) construed the term "hypnobo" to emphasis a similar phenomenon. Kirsch & Lynn (1997) proposed that placebo effects may have similar substrates of human behaviour that are experienced automatically or involuntarily like hypnotic responses. Also, within placebo, there is, like HHIs in hypnosis, good placebo responders (GPRs; Raz, 2005). Thus, Raz (2005) has suggested that the features of HHIs may overlap with those of GPRs, especially as identification of a specific Catechol-O-methyltransferase (COMPT) polymorphism has been found to correlate with hypnotisability; and may tap into similar associations with GPRs. As placebo response is improved by expectation, suggestion, and elements of anticipation and prediction, it is practical to suggest that some form of positive correlation between GPRs and HHIs exist (Raz, 2005). Consequently, prominent theoreticians have suggested that it would be helpful to apply hypnosis to clinical and medical settings for its placebo value in engendering positive expectations (Kirsch, 1997; Raz, 2007).

In contrast, Lifshitz et al. (2017) have reported that a robust correlation between hypnotic suggestibility and placebo response remains elusive (e.g., Lund et al., 2015; Parris, 2016; Raz, 2007). Furthermore, Liftshitz et al. (2012), Bendetti (2010) and Benham et al. (1998) have argued that there are different types of suggestibility. Hypnosis involves aptitude suggestibility, while placebo involves attitudinal suggestibility (which includes expectation and beliefs), thus expectancy

plays a greater role in placebo than hypnosis (Bendetti, 2010; Benham et al., 1998). In support of differences between hypnosis and placebo, Hull (1993) suggested that measures of placebo suggestibility (which are indirect suggestions via false statements inducing gullibility) are different to measures of hypnotic/imaginative (direct) suggestibility; which also involves dissociation (Bernstein & Putnam, 1986; Woody & Bowers, 1994; Terhune et al, 2011), and absorption (Cadlena & Spiegal, 1991). Accordingly, Horton and Crawford (2004) found that HHIs experience greater hemispheric asymmetry during tasks under hypnosis, compared to LHIs, which they attributed to traits of proneness to fantasy, motivation and expectation within HHIs; however, no such individual differences have been observed in placebo responders (Parris, 2016).

While hypnotic/imaginative suggestibility appears to be a stable trait (Piccione, Hilgard, & Zimbardo, 1989), placebo suggestibility, in contrast, is unstable and can affect research outcomes due to differences in, for example, the pharmaceutical properties suggested (Whalley, Hyland & Kirsch, 2008). This is further supported by Lifshitz, Sheiner, Olson, Theriault & Raz (2017), who reported that placebo responses can be inconsistent, unreliable and tenuous, due to the involvement of complex interactions between context (e.g. situational variable and expectations) and individual traits (Darragh, Booth & Considine, 2015; Horing, Weimer, Colloca & Enck, 2015). Furthermore, McGlashan, Evans and Orne (1969) reported that hypnotic analgesia not only included more processes than expectancy (placebo has been shown to be entirely mediated by expectancy; e.g., Kirsch, 1999); it was also more powerful than placebo as an analgesia, and consequently they suggested that the two phenomena are unrelated. However, McGlashan et al. failed to consider placebo's differing effectiveness (e.g. the pharmaceutical properties suggested). For example, placebo morphine is more effective than a Darvon Placebo pill (Evans, 1974), which McGlashan et al. used as a placebo control. Thus, as Evans suggested, weakened the placebo effect, compared to the stronger treatment.

Interestingly, research by Milling, Allen & Reutenaur (2005) found placebo analgesia to be less effective than hypnotic analgesia, except when placebo treatment was undertaken after standard hypnosis. Milling et al. compared three counterbalanced treatments against a control: firstly; non-hypnotic imaginative pain analgesia

suggestion (imaginative suggestions administered to within-subjects' participants, without mentioning hypnosis or having a standard induction). Secondly; participants were given a standard hypnosis treatment and thirdly; participants received a topical placebo treatment. Milling et al. found non-hypnotic imaginative suggestion and standard hypnosis to be equally effective as a pain analgesic, and more so than placebo analgesia and the control condition. However, when placebo was given after standard hypnosis, if became as effective as standard hypnosis, and Milling et al. attributed this as being due to a 'carryover' of suggestion from the hypnosis treatment (imagining that their hand was insensitive and numb).

Thus, it would seem there is a debate between theorists, as to whether hypnosis and placebo are a similar phenomenon. Since technological and methodological advancements, numerous theories and investigations have been undertaken to ascertain the exact cognitive mechanisms underpinning placebo, and particularly hypnotic response, especially in the last two decades (see reviews by Paris, 2016b; Landry et al., 2017), to see if hypnotic responding is reliant on frontal lobe function. Research behind placebo and hypnosis, and its effect on pain relief, could indicate which form of treatment is likely to benefit particular patient groups (Parris 2016a). For example, impaired PFC Alzheimer's or stroke patients might benefit from hypnotic analgesia, having lost that very important, but often overlooked contributor to pain control: The placebo effect (Benedetti et al., 2006). Indeed, one potential area of difference between hypnosis and placebo effects is their reliance on the frontal lobes of the brain.

1.5 Placebo and the Prefrontal Cortex

As the placebo effect is influenced by suggestion, it is not surprising that current literature strongly indicates that normal or increased functioning of the PFC is required for the placebo effect to take place (Benedetti, 2010; Krummenacher et al., 2010). Benedetti also suggested that if there is reduced or impaired functioning of the PFC then there will be little or no placebo effect. Consequently, findings have also suggested that successful placebo analgesic response requires normal or increased functioning of the brain's frontal areas (Benedetti, 2010). Within the PFC, the Dorsal Lateral Prefrontal Cortex (DLPFC) has been commonly linked to expectation-related placebo analgesia (e.g. Pariente, White, Frackowiak & Lewith, 2005; Wager et al., 2004), which

also plays an important role in attention-related and cognitive pain regulation (e.g. Lorenz, Minosham & Casey, 2003; Graff-Guerrero et al., 2005). The DLPFC controls pain perception through modulation of corticocortical and cortico-subcortical pathways and drives the placebo effect through involvement in updating and maintaining expectation (Lorenz, 2015). Expectation mechanisms tap sensory experiences, especially in relation to pain processing (Weich, Ploner & Tracey, 2008); thus, predominately linking clear involvement of the right hemisphere, with the right PFC suggested as being the dominant area for controlling central opioid release in pain-response (Graff-Guerrero et al., 2005; Wager & Atlas 2015), and for mediating placebo response (Leuchter, Cook, Witte, Morgan & Abrams, 2002; Lieberman et al., 2004; Pariente et al., 2005).

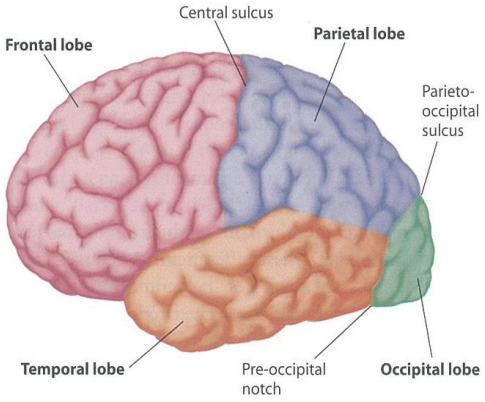

Figure 1 Frontal Cortex Divisions (Gazzaniga, Ivry & Mangun 2002).

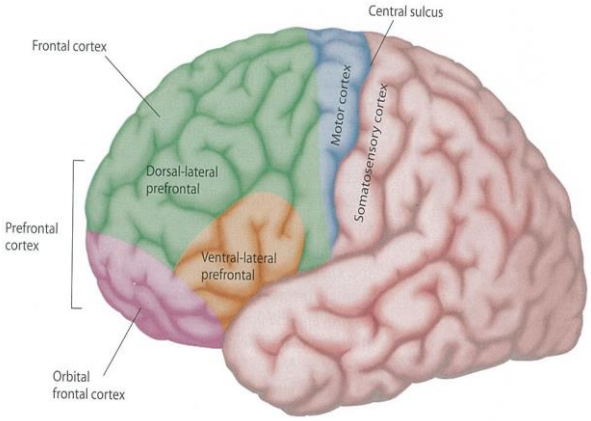

Figure 2 Four Lobes belonging to the Cerebral Cortex (left, Hemisphere lateral view). (Gazzaniga, Ivry & Mangun, 2002).

A novel, between-subjects study by Krummenacher et al. (2010) found that repetitive transcranial magnetic stimulation (rTMS: an emerging experimental tool, once applied to targeted cortical regions depresses cortical excitability), applied to the left and right DLPFC completely blocked placebo analgesic pain response. In contrast, patients in the sham (placebo analgesia) stimulation condition, believing that they had received rTMS, were able to endure pain heat stimuli for longer, at both pain threshold (pain onset) and pain tolerance levels (maximum pain endurance level), which indicated that the prefrontal executive control is crucial for triggering descending pain control.

Interestingly, the findings suggested that expectation induced placebo analgesia is a function of both left and right hemispheres within the PFC, which Wager et al., (2004) also found during their fMRI study. In contrast, Egorova et al., (2015) have been able to modulate a conditioned placebo effect through tDCS (transcranial direct-current stimulation), by altering the excitability of right DLPFC involvement. Further involvement of the right DLPFC has been found by Graff-Guerrero et al. (2005), Leuchter et al. (2002), Lieberman et al. (2004), Pariente et al. (2005) and Wager & Atlas (2015). Thus, it would seem that the mechanisms behind placebo involves a clear involvement of the PFC, more specifically, evidence has underpinned the processes of the right DLPFC in placebo over the left DLPFC. In contrast, Krummenacher et al., (2010) and Wager et al., (2004) have found evidence for both left and right DLPFC involvement in placebo responding.

1.6 Hypnosis and the Prefrontal Cortex

Due to their similarities, it is not surprising that hypnosis mechanisms, like placebo mechanisms, have been linked to the cognitive process of the FEFs and the PFC, but with less clear involvement (Parris, 2016b; Landry, Lifshitz & Raz (2017). Theories underpinning the mechanisms of hypnosis are many and varied, and have included top-down involvement, comprising neurocognitive processes that feature frontal brain structures, such as cognitive monitoring, attention, and executive control (Gruzelier, 2006; Raz, 2007). For example, the central executive network (CEN) and salience network (SN), are two large areas within the frontal brain that are fundamental to higher-order cognition, with the DLPFC within the PFC being a main component of the CEN (Landry et al., 2017). Other features of top-down processing include the activity of the anteria insula (AI) and anterior cingulate cortex (ACC), both fundamental parts of the SN (Landry et al., 2017). It is proposed that these networks are responsible for the feelings of absorption (e.g., Raz, 2005) and sense of automaticity (responses appear to happen on their own), experienced during hypnosis (e.g., Dienes & Perner, 2007). In contrast, an alternate explanation has suggested that hypnotic response is due to a deactivation in an essential part of the frontal node of the default network (DN), called the medial prefrontal cortex (mPFC) (e.g., Oakley & Halligan, 2013; Landry & Raz, 2015; Raichle, 2015). The DN is a system that controls self-generated thoughts, social-cognition, internal attention and mind-wandering (Christoff, Gordon, Smallwood,

Smith, & Schooler, 2009; Mason et al., 2007). It is proposed that the connectivity and activities between and within these networks are responsible for the top-down strategies, mental absorption, reduced episodes of mind wandering and a reduction in awareness of irrelevant events, associated with hypnotic responses (Landry et al., 2017).

Two further theories have suggested two ways that the functioning of the PFC impacts the degree of suggestibility within hypnosis. The first of these theories is called Cold Control Theory (CCT; Dienes & Perner, 2007). CCT suggests that successful hypnosis occurs due to decreased (inhibited) functioning within the whole of the PFC, and that it is this decrease in functioning which allows for successful hypnotic suggestibility to occur in HHIs. Thus, hypnosis occurs via conscious cognitive monitoring or unconscious executive control. CCT involves metacognition (e.g., a critical awareness of how we think about our own thinking and learning, Metcalfe & Shimamura, 1994), and the left and right DLPFC (e.g., Fleming, Huijgen, & Dolan, 2012; Fleming, Ryu, Golfinos, & Blackmon, 2014); which interferes with responses, selection and assessment over appropriate intent to thought and action (Dienes, 2012), thus reducing cognitive and behavioural ownership (Lush, Naish, & Dienes, 2016). Therefore, it is for this reason that CCT would predict that HHIs would perform better during hypnotic analgesia than LHIs (e.g. Geers et al., 2015; Montgomery & Kirsch, 1996), and CCT would also predict that HHIs already have reduced frontal control at baseline (prior to hypnosis) and not just during hypnosis (Dienes & Hutton, 2013; Lynn & Green, 2011).

The second theory is called Dissociated Control Theory (DCT; Woody & Bowers, 1994). In contrast, DCT suggests that successful hypnosis occurs due to a decrease in the left PFC function only. Consequently, hypnosis occurs via a decoupling process between the anterior cingulate cortex (ACC; responsible for conflict monitoring (Jamieson & Woody, 2007), and the left DLPFC, which increases the activity in the ACC and reduces the communication between monitoring and executive systems (Egner et al., 2005). This decoupling process also reduces behavioural flexibility, thus increasing frontal activity and contention scheduling, leaving a level of PFC guidance (Parris, 2016b). Consequently, DCT would also predict that HHIs would perform better during hypnotic analgesia than LHIs (e.g. Geers et al., 2015; Montgomery & Kirsch, 1996). In further contrast from CCT, DCT predicts that HHIs and LHIs have similar

activity in the DLPFC at baseline and during hypnosis (found during the Stroop task; Stroop, 1935) and that HHIs become more suggestible due to the decreased functional connectivity and the increase in the activity of the ACC (Egner et al., 2005).

Evidence supporting a decrease in global PFC (DCT; Woody & Bowers, 1994), has been provided by Terhune, Cardena and Lindgren (2011), using groups of participants who scored either low or high on the Dissociative Experiences Scale (DES; having certain experiences of clinical dissociation in their everyday life; Bernstein & Putnam, 1986). HHIs, who were also high dissociators, were shown to exhibit reduced cognitive control (connectivity) during hypnosis (Parris, 2016b). This is an important finding, potentially indicating that during hypnosis, the mechanisms belonging to participants with highly dissociative tendencies were mediating increased connectivity and decoupling of the DLPFC and ACC (Parris, 2016b).

Further support for a decrease in the left PFC function (CCT; Dienes & Perner, 2007) affecting hypnosis was found by Dienes and Hutton (2013). Dienes and Hutton used rTMS to test the brain mechanisms underlying hypnotic responses, in a within-subject's condition (all patients undertook two separate conditions), between two brain sites: the left DLPFC and the vertex (placebo control site). They found that rTMS to the left DLPFC, at baseline, actually increased hypnotic response by 6% in medium hypnotisable individuals (MHIs), and postulated that this was due to a component of diminished function (inhibition) within the PFC. Although, this study adds further support to the centrality of the left DLPFC and impaired metacognitive abilities during hypnosis, a review by Parris (2016b) specifies that CCT still requires further corroboration. Interestingly, Dienes & Hutton (2013) found that patient expectancies were the same for both conditions; therefore, hypnotic suggestibility was not determined by expectancy. This was a novel finding, as expectancy-based theories (among other theories), have played a central role in elucidating the phenomena behind hypnotic suggestibility.

Further support for inhibition of the frontal lobes (CCT; Dienes & Perner, 2007), affecting the left PFC within hypnotic responding, was found by Egner, Jamieson and Gruzelier (2005). During Stroop task performance (a left PFC task), HHIs exhibited more inhibition than LHIs as they became hypnotised which indicated left hemisphere functioning. The Stroop task is one of the most widely used inhibitory

tasks in neuropsychology (patients with PFC lesions have an inability to perform well in EF tasks that require inhibition), and requires the participant to verbally name the colour of the ink that a word is printed in, whilst ignoring the actual word (e.g. the word 'blue' is written in red ink and thus the patient's correct, inhibitory response would be to name the incongruent colour 'RED' instead).

Further support for left hemisphere function during hypnosis have also been reported by Kosslyn, Thompson, Costantini-Ferrando, Alpert & Spiegel (2000) and Laria, Fox, Waite, Aharon and Barton (2008). Interestingly, Laria et al., (2008) demonstrated that neural correlates of colour perception were activated in the fusiform gyrus (a left hemisphere mechanism which also processes faces and is located next to the lingual gyrus), when participants were focusing on colour suggestion.

A further distinction was made by Gruzelier (2014) who found that hypnosis was firstly underpinned by a left hemisphere preference in HHIs, later switching to a right hemisphere preference. Gruzelier showed that when individuals listened to the hypnotist, fixated their eyes on a visual point, and then closed their eyes to relax, the left (including the DLPFC) hemisphere was activated (and included the processes of inhibition, dissociation or uncoupling). This processes then led to the 'letting go' element for the HHI in the hypnotic induction, as the brain, in parallel, let go of its planning and EF (inhibitory process), towards a right hemisphere preference, which then brought on the relaxed, passive imagery state in the HHI. In contrast, LHIs did not 'let go' and undergo the inhibitory process, which Gruzelier proposed was due to concern for loss of control, believing that, for example, hypnosis had consequences.

Consequently, the contradictory evidence surrounding the function of the FEFs within hypnosis and at baseline, has made it difficult to interpret the findings highlighted by DCT (Woody & Bowers, 1994) and CCT (Dienes & Perner, 2007). The differences between HHIs and LHIs both at baseline and during hypnosis, on EF tasks such as the Stroop task (Stroop, 1935) further confuses matters. As previously mentioned, HHIs have been found to exhibit weakened frontal control, and greater Stroop conflict (Stroop, 1935) than LHIs, both at baseline, suggesting reduced function of the DLPFC is potentially independent of hypnosis, which may potentially facilitate the induction of hypnosis (Parris, 2016a) and under hypnosis (Blum & Graef, 1971; Dixon, Brunet, & Laurence, 1990; Dixon & Laurence, 1992; Farvolden & Woody,

2004; Lynn & Green, 2011). In contrast, other research has found that HHIs and LHIs show no differences in performance on the Stroop task at baseline or under hypnosis, except for an increase in the ACC during hypnosis for HHIs (Egner et al., 2005), breaking the communication of the monitoring and executive systems. Importantly, studies with greater sample sizes found no performance differences between HHIs and LHIs at baseline on tasks thought to index frontal lobe function (Dienes et al., 2009; Varga et al., 2011). Consequently, Parris (2016a) suggested that the difference in results may be due to the researchers' methodology, using tasks which may not clearly involve the DLPFC or failing to titrate task difficulty.

Thus, a current review and meta-analysis by Landry et al., (2017) reported that the large variation in hypnotic methodological standards, coupled with the complex nature of hypnosis, has made it difficult to generalize which mechanisms are specifically associated with hypnosis. Furthermore, they propose that the lingual gyrus (a left hemisphere function, not within the PFC but at the back of the head, in the occipital lobe), may play a crucial role in hypnotic responding, due to it enhancing hypnotic mental imagery. A further review by Parris (2016b) also highlighted that it was difficult to make a clear conclusion to the exact nature of the role in FEFs in hypnosis, as current literature appears mixed.

While the mechanisms underpinning placebo responding potentially point to the right hemisphere of the PFC, the involvement of the PFC within hypnotic responding, however, remains far less clear (Parris, 2016b; Landry et al., 2017). Although, there is a large quantity of research pointing to both left and right hemispheres for supporting hypnotic suggestibility, there is little consistency in the findings (Parris, 2016b). However, the results from the research with better controls and larger sample sizes loosely points to the left hemisphere being the more potentially dominant area for supporting hypnotic suggestibility (e.g.; Dienes and Hutton, 2013; Egner, Jamieson & Gruzelier, 2005; Laria et al., 2008; Kosslyn et al., 2000).

1.7 The Present Research

Although it has been proposed that the role of the PFC and FEFs play a role in the neural mechanisms underpinning the phenomena of hypnosis and placebo (e.g., Landry, Lifshitz & Raz, 2017; Parris, 2016a; 2016b), there is evidence that their

mechanisms of action may be different (Parris, 2016a). While placebo effects have been found to rely on the PFC (Benedetti, 2010), it has been less than clear the conclusion of the involvement of the PFC in hypnotic suggestibility, and it may be that hypnosis and placebo effects could be differentiated by the involvement of the DLPFC (Parris, 2016b). Additionally, there are variations to placebo and hypnotic suggestion; hypnotic suggestion involves direct suggestion, while placebo suggestion involves indirect suggestion (e.g. gullibility and false statements) (Hull, 1993). It may be that the PFC (which is a large area in the brain) only plays a role in indirect placebo suggestions (Hull, 1993). As noted previously, the rTMS studies of Dienes and Hutton (2013) found that rTMS to the left DLPFC inhibited its function, in line with CCT (Dienes & Perner, 2007), and increased hypnotic response by 6%, while Krummenacher et al. (2010), found that rTMS to the left and right DLPFC disrupted expectancy-based placebo response. These two findings, from two separate studies, suggest a contrasting role for the PFC and DLPFC, in relation to placebo and hypnotic responses. Although these two studies appear to advance understandings on the neural mechanisms of the PFC, it is important to note that both these studies used contrasting methodology (neither study applied rTMS at the same time-points or for the same time-period in their methodology e.g. Dienes & Hutton used rTMS before hypnotic induction/suggestion and Krummenacher et al., used rTMS after placebo-analgesia suggestion was given). Consequently, it is difficult to compare the two findings directly (Parris 2016a).

Thus, the aim of this research is to investigate if placebo analgesia and hypnotic analgesia are reliant on frontal lobe function. Moreover, the research aims to ascertain whether there is an effect of hemispheric laterality within the PFC, on the experience of either forms of analgesia, by using the findings based on Cipolotti et al.'s (2016) left and right EF hemisphere research (see also Glascher et al., 2012; Geddes, Tsuchida, Ashley, Swick & Fellows, 2014). Using patients with brain lesions, Cipolotti et al. found two unrelated EF tasks that were specifically related to the left PFC cortex (the Stroop Task; Stroop, 1935) or the right PFC (the Hayling Task; Burgess & Shallice, 1996). They undertook cognitive (30 patients) and neuroimaging investigations, specifically voxel-based lesion symptom mapping (VLSM; with 58 patients) on patients with focal unilateral PFC lesions (due to a brain tumor or cerebrovascular

accident) located in the frontal lobes and compared them against a control condition (60 healthy patients). Cipolotti et al. demonstrated that the left PFC is the critical area involved in inhibition (an ability to inhibit impulses and select the appropriate behavioural responses to information, action or stimuli; Diamond, 2003), interference control, and response conflict processes in the Stroop Task (1935).

Cipolotti et al., (2016) found that inhibitory errors were also made on the Hayling Sentence Completion task (Burgess & Shallice, 1996). The Hayling is thought to assess response inhibition/suppression along with strategy generation and requires participants to complete a sentence using words that are not related to the sentence topic, for example 'Bournemouth can be a very busy…' could be completed by saying for example, the word...'apple' instead of the appropriate word 'place (or town)'. Instead, participants with frontal-lobe damage might have produced suppression errors, due to an inability to generate the correct strategy and answer with the appropriate word 'town', instead of 'apple'. In contrast to the Stroop, the Hayling Task showed an effect of right PFC lateralization (Cipolotti et al., 2016).

Importantly, Cipolotti et al.'s (2016) study also showed that the Hayling and the Stroop tasks were not related, and unlike many other EF tasks they were not entirely mediated by fluid intelligence (fluid intelligence has been found to be impaired after frontal lesion damage and is positively correlated with executive function tests; Duncan et al., 1996). Fluid intelligence is the ability to reason, solve novel problems, identify patterns and relationships within these problems, and extrapolate using logic (Jaeggi, Buschkuehl, Jonide & Perrig, 2008). It has been proposed that general fluid intelligence (*g*), which lies closely with fluid intelligence (Carroll, 1993), sits within the multiple demand network (MDN; a large PFC parietal network), and has been linked with an array of cognitive process identified during functional imaging tasks (e.g. Woolgar et al., 2010). Furthermore, studies have shown that fluid intelligence is a marker of general frontal lobe function (e.g.; Duncan et al., 1995; Woolgar et al., 2010), and a global PFC function (Parris, 2016b).

Cipolotti et al. (2016) suggested that the Hayling and the Stroop tasks tap into diverse, anatomically defined components of inhibition within EF processing, between patients with left (who were impaired on the Stroop task but not the Hayling), and right (who were in contrast impaired on the Hayling task and not the Stroop) frontal lesion

locations. Demonstrating that Fluid IQ taps global PFC function may make it possible to identify if participants are using global PFC and/or left or right hemisphere function, when tested using the Hayling and Stroop Tasks (Cipolotti et al., 2016), alongside hypnotic and placebo analgesia. Consequently, this research also aims, through Cipolotti et al.'s findings, to see if placebo analgesia and hypnotic analgesia are potentially reliant on global frontal lobe function through the use of Fluid IQ testing (Wechsler, 2008).

Using aspects of Cipolotti et al.'s (2016) methodology theoretically, may provide tentative evidence for hemispheric laterality within the PFC, for hypnosis and placebo analgesia. Theoretically, it may appear that the linguistically-dependant hypnotic response may be more likely to rely on the left PFC **(**Dienes and Hutton, 2013; Egner, Jamieson & Gruzelier, 2005; Laria et al., 2008; Kosslyn et al., 2000), while the expectancy-dependent placebo response may be more likely to potentially rely on the right PFC **(**Graff-Guerrero et al., 2005; Leuchter et al., 2002; Lieberman et al., 2004; Pariente et al., 2005; Wager & Atlas 2015).

Consequently, the cognitive EF tasks of the Hayling, Stroop and Fluid IQ were used as measures of left, right or global PFC inhibition functioning at baseline. It was the intention specifically to measure PFC function at baseline because we were looking to identify the baseline predictors of hypnotic and placebo analgesia. Accordingly, using the Stroop task as a predictor of left PFC inhibition function would fit well with CCT (Dienes & Perner, 2007), which predicts that inhibition of the left PFC is required for successful hypnotic suggestibility to occur (Dienes & Hutton, 2013). In contrast, both the Hayling and the Stroop task would fit well with DCT (Woody & Bowers, 1994), which advocates that baseline left and right PFC function would be already be relatively impaired and thus more susceptible to hypnosis and hypnotic suggestions. According to the DCT a lower performance on both these tasks would be a precursor for high hypnotic suggestibility. Additionally, DCT theory would predict that a lower Fluid IQ score would increase hypnotic suggestibility because Fluid IQ is a reasonable proxy measure for general frontal lobe function (Parris, 2016b). Since DCT claims that a lower functioning frontal lobe would make someone more suggestible, a lower Fluid IQ score would then relate to higher suggestibility. CCT would be relatively

silent on the role of Fluid IQ because their predictions are based on left PFC functioning only.

In relation to placebo effect, which needs normal or increased PFC functioning, any reduction in PFC functioning would potentially predict that a lower fluid IQ score would result in a smaller placebo effect (Benedetti, 2010). As the Stroop task is a left DLPFC task and the placebo effect has been related to the right DLPFC, this study is not expecting the Stroop task to predict the magnitude of placebo analgesia. However, the Hayling task as a predictor of right DLPFC may potentially predict the magnitude of placebo analgesia.

Thus, research behind placebo and hypnosis, and its effect on pain relief, may indicate which form of treatment is likely to benefit particular patient groups (Parris 2016a). Therefore, further research is needed to compare and contrast the role of FEFs in hypnotic and placebo responses (Parris, 2016a; Parris, 2016b). Based on the findings by Cipolotti et al. (2016), performance on the Hayling Task (a right frontal, dominant task) may theoretically predict the magnitude of placebo analgesia, while performance on the Stroop Task (a left frontal, dominant task) may theoretically predict the magnitude of hypnotic analgesia. These predictions could potentially be revealed through hypnotic and placebo analgesia, measured through the use of the Cold Pressor Test (Rash & Campbell, 2014), a commonly used test for pain- threshold and pain-tolerance, as it induces and mimics chronic pain (Campbell, Holder & France 2006). Fluid IQ will be measured using the WASI Fluid Intelligence Test (Wechsler, 1939; 2008) to identify if placebo analgesia and hypnotic analgesia have any potential reliance on global frontal lobe function.

2. Method

2.1 Design

A within-subjects' experimental design was used. Performance on three tests of executive function were used; the Hayling Task, the Stroop Task and the WASI Fluid Intelligence Test. The dependant variables (DVs) were participants' pain-threshold and pain-tolerance scores using the Cold Pressure Test (CPT), during three counterbalanced conditions: 1) After receiving a hypnotic suggestion for analgesia; 2) After receiving a placebo analgesia (hand cream); 3) After receiving a "cleansing"

hand cream (control). Additionally, participant's CP data was converted to achieve hypnosis and placebo pain threshold and pain tolerance scores as follows: 1) All control threshold scores were subtracted from hypnosis threshold scores for hypnosis analgesia threshold; 2) All control tolerance scores were subtracted from hypnosis tolerance scores for hypnosis analgesia tolerance; 3) All control threshold scores were subtracted from placebo threshold scores for placebo analgesia threshold; 4) All control tolerance scores were subtracted from placebo tolerance scores for placebo analgesia tolerance.

2.2 Participants

A group of 54 participants were recruited from either Bournemouth University's experiment participation system (for 2 credits, or for £15.00) via advertisements placed within the university campus. All participants were healthy students aged between 18-48 years (M= 21.93, SD = 5.6) of which 27 were males.

Exclusion criteria included: those suffering with a heart condition, or any persons taking pain medication for pain conditions (e.g. amitriptyline), as the medication prescribed for both these conditions may have affected pain tolerance levels on the CPT (Geers et al., 2015; Washington, Gibson & Helme, 2000). Recommendations were also made to exclude: those who have suffered a stroke, those suffering with schizophrenia, bi-polar disorder or epilepsy, those taking anti-psychotic and/or anti-depressants and/or anxiety medication. Participants were also told to exclude alcohol for 24 hours prior to testing, as well as excluding smoking, drinking coffee/caffeinated sports drinks and food for two hours prior to testing, as these may all have affected EF performance (e.g. Geers et al., 2015; Guillot, Fanning, Bullock, McCloskey & Berman, 2016; Soar, Chapman, Lavan, Jansari & Turner, 2016; Washington, Gibson & Helme, 2000). Additionally, participants who had participated in research using the CPT before were also excluded, due to prior experience negatively effecting novel placebo-expectation pain reduction (Geers et al., 2015). The experiment was approved by the Departmental Ethics Committee at BU.

2.3 Materials and Equipment

Cold pressor test apparatus (CPT):

The cold pressor (CP) consisted of a Coleman 36 QT Cooler, containing ice-cold water that contained a large circular bowel that had a circumference large enough for a hand to be rested in, with fingers spread. The bowl was also used to keep the netting and ice pushed towards the inner sides of the CP, thus stopping the ice from touching the participants hand whilst it was immersing in the water. The temperature of the water was maintained at 2 degrees Celsius (C) and did not fluctuate by more than 0.5 degrees C, as small changes could result in pain response variations (Mitchell, MacDonald & Brodie, 2004). Additionally, a circulatory water pump by Fluval SEA CP1 (Circulation Pump 1000LPH) was used to maintain the desired temperature, and to prevent a microclimate of warm water building up around the hand (Baeyer et al., 2005). The ice-water level inside the CP was high enough for the hand and wrist to be fully immersed (Baeyer et al., 2005).

The CP is a task where immersions are often timed up to a maximum of 180 seconds (Baeyer et al., 2005). Two time-points are recorded once the hand is immersed; Pain-threshold: first initial onset of cold discomfort felt (timed from 0 seconds) and Pain-tolerance: maximum time hand kept immersed (timed from 0 seconds). Thus, the DV used for the CPT were participants' pain-threshold and pain-tolerance scores, using difference scores. Consequently, successful placebo and hypnotic analgesia would require participants to leave their hand immersed for as long as possible (maximum 180sec).

Blood Pressure and Heart rate:

Blood pressure (systolic and diastolic) and heart rate were measured using an Omron M2 Basic Intelli Sense Automatic upper arm blood pressure monitor, as a health and safety check.

Hand Temperature:

Hand temperature was measured using an Acxeon Non-Contact Infrared Forehead-body Thermometer, Digital Laser, Temperature Measurement Gun and was used to take temperature reading of the participant's hands (Finlay & Anil, 2016). A standard

size hot water bottle was also used after each immersion; wrapped in to a soft, small blanket that participants could slip their hand/s inside to warm up, in order to prevent a cumulative cooling effect on the hands, due to repeated immersions (Mitchell, MacDonald & Brodie, 2004).

Fluid Intelligence:

The Block Design and Matrix Reasoning Test were from the Wechsler Abbreviated Scale of Intelligence II (WASI; Wechsler, 1939; 2008), and were used as a measure of global, frontal lobe function. Each participant was scored based on age, to match ability evenly. This was a timed test, with 45 seconds being allowed for each item on the test. Two separate tests were given: 1) block design (BD) and 2) matrix reasoning (MR). Each correct answer scored one mark. The manual stated that testing should be discontinued when the participant has made two consecutive incorrect answers for the BD and three consecutive incorrect answers for the MR. MR and BD scores were added up and combined to give a total raw score, which was then converted to a standardised scaled score, using the appropriate age category, via the instruction manual. A standardised score of 100 represented the midpoint of the average range. Thus, the DV was participants' combined MR and BD standardised scaled score. Consequently, the higher a participant's Fluid IQ Score the better their performance.

The Stroop Task (Stroop, 1935):

The present study used the Golden and Freshwater (1998; 2002) paper version of the Stroop, which consisted of three A4 pages; page one: five columns of 20 words randomly written in 'RED', 'GREEN' and 'BLUE', and printed in black ink (Word Score). Page two: five columns of 20 coloured crosses 'XXXX' randomly printed in red, green and blue ink (Colour Score). Page three: five columns of 20 coloured words, 'RED', 'GREEN' and 'BLUE', written randomly in incongruent colours to the words e.g. the word 'GREEN' written in blue ink (Colour-word Score). Participants had 45 seconds to read out loud one page at a time. If the participant had finished the page they were reading from, before the 45 seconds finished then they could re-read it. If any colours were incorrectly stated, then the researcher would say "No", and the participant had to read again correctly before moving on. The researcher marked each correct answer. Slower response times and/or frequent errors reduced a participant's

score. The raw scores for each of the three pages (Word Score; Colour Score; Colour-Word Score) were added up individually and then converted in to an Interference Raw Score, and then in to a T-Score using the tables provided in the instruction manual (which did not need to be corrected for education level or age). Thus, the DV, which used a difference score was participants' interference scores. Consequently, the lower a participant's Stroop Interference Score, the better their performance.

The Hayling Sentence Completion Task, Part 1 and Part 2 (Burgess & Shallice, 1996):

This test is thought to assess response inhibition/suppression along with strategy generation. Part 1: consisted of asking participants to complete 15 sentences using words that are related to the sentence topic, for example 'Bournemouth can be a very busy…' could be completed by saying the word 'place'. Part 2: consisted of asking participants to complete 15 sentences using words that were unrelated to the sentence topic, for example 'Bournemouth can be a very busy…' could be completed by saying the word...'apple' instead of the appropriate word 'place (or town)'. After the researcher read a sentence, the participant had to say the missing word as quickly as possible. The researcher made a note of each answer and the time taken, as both were part of the scoring criteria. Individuals with frontal lobe damage may produce suppression errors, and answer with the appropriate word 'town', instead of 'apple', and often they may have longer response times, consequently reducing their scores.
Thus, responses to both Part 1 and Part 2 were timed in whole second units by the administrator and converted in to a scaled score. Then, any error scores made in Part 2 (category A and category B errors) were calculated and transformed in to a scaled score. Part 1 and Part 2 scores were then calculated and converted to an overall Hayling scaled score (see manual). Thus, the DV was the overall Hayling scaled score. Consequently, the higher the individual's Hayling Score, the poorer their performance.

Placebo Analgesia:

The placebo hand-cream was contained in a white pump-dispenser labelled 'Travarican: Approved for research purposes only' and contained E45 cream mixed with Conotrane Soothing Cream and Thyme Oil (ThymusVulgaris), by Health Aid, for a medicinal smell, and red natural food colouring to add a hint of colour.

Control Cream:

The control cream was an E45 cream with no additional odour or colouring, placed in an identical dispenser to the placebo-analgesia cream, and was labelled 'Soft Clean: Lotion and Hand Cleanser.

Hypnotic Analgesia Suggestion:

The participants, prior to immersing their hand in the ice-cold water, were given an application of 'Soft Clean: Lotion and Hand Cleanser' (see above), to match the other two conditions, for consistency. During preparation, the participants were told that "hypnosis is a very powerful tool and is now used on Cancer patients to reduce pain. It is also used by dentists in dentistry, instead of anaesthesia, and in operations by surgeons, again instead of anaesthesia". During the CPT the participants were given the suggestion "the hand is insensitive to pain and no pain sensation will originate from it." Participants were led to believe that the hypnotic induction and script for the hypnotic analgesia CPT were taken from an Oxford Short Induction Script, to create a more professional impression. However, the induction and hypnotic suggestion were partially adapted from The Stanford Hypnotic Susceptibility Scale – Form C (SHSS: C; Weitzenhoffer & Hilgard, 1962) and also from a passage in Casiglia et al.'s (2007) study (see Appendix D).

Each time the researcher applied a cream, the participants' lower wrist, arm and hand was rested comfortably on an ABLE2 UK LTD cushioned lap rest, covered over with a hand-towel and a large sheet of kitchen towel (which was changed each time a cream was applied).

2.4 Procedure

A pilot study was first conducted. It was decided that the CP container was not adequately insulated to keep the ice-water from melting, nor was the positioning of it appropriate for three alternate handed immersions. There was also a lack of space for the researchers to move appropriately around the participant and the CPT equipment. Consequently, the room was re-arranged to make more space. The container was replaced with a blue Coleman 36 QT Cooler-box, which kept the ice-water chilled for longer. Additionally, the container was placed appropriately on to a large, high-backed chair, where the height was appropriate for the CPT, and also the chair was appropriate

to wheel safely behind the participant, to either their left or right-hand side, ready for their hand to be immersed. A second pilot was undertaken, which ensured that all the new changes ran appropriately and smoothly.

Upon arrival, participants were greeted by two researchers and asked to read the information sheet about the study (see appendix A), and if they had any questions about the research. Participant's filled in a participant details form, also asking them to report which was their dominant hand (see appendix B) and to confirm again that they met the inclusion criteria. Participants were then asked to read and complete the consent form (See appendix C). In order, to help participant's confidence with the EF tasks, the 2nd researcher told them that the research was looking for individual differences, and however they performed on the tasks was appropriate. Participants undertook the EF tasks with just the 1st researcher (as instructed by the EF manuals), and the 2nd researcher left. Participants undertook the EF tasks in the following order: WASI Block Design; the Hayling Task; the WASI Matrix Reasoning; the Paper Stroop Task (the researcher followed the written instruction and practise examples given in each EF guidance manual, as best practise, with the participant).

Participants were randomly allocated into 6 counterbalanced conditions as follows: 9 participants into the placebo analgesia/control/ hypnotic analgesia condition; 9 participants into the placebo analgesia/ hypnotic analgesia/ control condition; 9 participants into the control/placebo analgesia/hypnotic analgesia condition; 9 participants into the control/hypnotic analgesia/placebo analgesia condition; 9 participants into the hypnotic analgesia/placebo analgesia/control condition and finally, and finally, 9 participants into the hypnotic analgesia/ control/placebo analgesia condition. The hand which participants used for the CPT was also randomised, and alternated to deter practise-effect, and the build-up of coldness to a single hand (von Bayer et al., 2005) as the CPT was used 3 times during the experiment (placebo analgesic condition, hypnotic analgesia condition and control condition). Participants were tested individually.

When the participant had finished being tested, the 2nd researcher returned and checked the temperature of the CPT, making any adjustments to the temperature, as necessary, to maintain it at 2 degrees Celsius (C). The participant was then invited to sit down at a table specifically prepared for the CPT. BP, HR and hand temperature

were recorded for a baseline reading. Participants were then instructed by the 2nd researcher that there were two time-points, following immersion, that needed to be recorded by the researcher; firstly *Threshold,* which was recorded in seconds starting from when the participant first placed their hand in the water, up until the point that they then informed the researcher that their first initial onset of cold discomfort had been felt. Secondly; *Tolerance,* which was recorded when the participant, due to cold discomfort, informed the researcher that they could no longer tolerate leaving their hand in the water and withdraw it immediately; or if the participant still had their hand in the water after the required 180 seconds had elapsed, then the researcher would request for the hand to be withdrawn. Participants were told that the maximum they could keep their hand in the water for each immersion was 180 seconds, and that they would undertake three, alternating hand immersions in total (one immersion for each of the three conditions). Participants were also told that the CPT task was not a competition, but was instead about individual differences, to make them feel more at ease. Participants were also instructed on how to place their hand flat against the inside of the bowel, with their fingers spread. The 2nd researcher, then asked the participant to repeat back the instructions, to fully check understanding

Following this, the 2nd researcher applied an application of hand-cream to the participant's hand (either left or right depending on hand counterbalancing), which was either placebo analgesia, hypnotic analgesia or the control hand-cream (dependant on condition counterbalancing). Each immersion was timed by the 1st researcher for pain-threshold and pain-tolerance measures, whilst checking and recording the participant's BP and HR. When the participant withdrew their hand at the pain-tolerance point, the 2nd researcher was on hand to wrap their hand in kitchen towel to dry off the ice-water, whilst the 1st researcher freed the participant's arm from the BP cuff (after which they could dry off their own hand). The participant was then asked to firstly squeeze their hands tightly into a fist, and then rub their hands together to warm their circulation naturally, for one minute. After each immersion, the participant's hand was warmed on a hot-water bottle for two minutes, or further if needed (one minute on each side of the hand). Briefly after the participant's hand temperature had cooled, it was re-checked again to make sure that it had returned to baseline.

Prior to the hypnotic-analgesia condition the hypnotist (who was the 2nd researcher), asked/checked with the participant what their understanding of hypnosis was, and addressed any concerns. The hypnotist then applied the 'Soft and Clean' control hand-cream (any excess moisture was removed) and attached the BP cuff (only for this condition) on to the participant. The BP cuff was detached from the monitor and loosely fitted to the arm so that the participant could rest their arms comfortably by their side, or on their lap ready for the induction. Participants were told that after induction, the cuff would be re-attached to the monitor ready for the CPT, and that during the CPT their BP and HR would be monitored. Consequently, it was suggested to the participant, by the hypnotist, that during induction, "the cuff being re-attached to the monitor and the sensation of the BP cuff tightening on your arm, will not disturb you or disrupt your thoughts, if anything it will make you feel *even more* relaxed, and you will be able to focus *even more* on *my voice* and *my word*s." The participant was then reassured that all they needed to do to start hypnotic induction was, "all you need to do is sit comfortably in the chair, in a relaxed position, focus directly on the target (the hypnotist indicated to a marked spot on the wall), and then listen and focus *on my words* and *my suggestions*. As you do, you may notice that your eyes start to feel heavy and that you want to close them; and that is OK. If you find that your eyes do not feel tired, then that is OK too, as I will guide you to close them later." The hypnotist then conducted the induction, after which they were given hypnotic suggestions (see appendix D).

Prior to the placebo analgesia condition, the participant was given an application of an inert analgesic placebo-cream, based mainly on the methodology by Montgomery and Kirsch (1996) and Geers et al. (2015). The placebo analgesia was pumped on to the participant's hand and massaged in by the 2nd researcher, who was wearing disposable gloves and a white lab coat. The participant was told by the 2nd researcher that "Travaricane is a very powerful analgesic cream, it has just a light clinical smell and is used by surgeons and GP's for stitches and injections, on the sensitive areas of the face. It is also especially useful, for example, on footballers and rugby player's during bodily injury, as it only takes 30 seconds to start working". The 2nd researcher then made exaggerated movements to really massage the cream in to the participants hands, making a special effort to cover the nails and in between the fingers, expressing

that “I don’t want to miss the nails and in between the fingers as they are also sensitive to the cold”.

Prior to the control condition, the 2nd researcher told participants that they were now going to have ‘Soft and Clean’ cream applied to their hand and that, “it does exactly what it says on the label and has absolutely no pain reduction properties whatsoever! It is just used as a control.”

When all three CP conditions had been undertaken and the participant’s hands were returned to their baseline temperature, the participants were thanked for their time and were debriefed by the hypnotist (see appendix E).

3. Results

The present study found that on average hypnotic analgesia was larger on both pain-threshold (*M*=78.83, *SD*=71.69) and pain-tolerance performance (*M*=111.07, *SD*=66.73) compared to placebo analgesia pain-threshold (*M*=13.72, *SD*=13.51) and pain-tolerance performance (*M*=78.72, *SD*=60.93) and control pain-threshold (*M*=10.06, *SD*=14.11) and pain-tolerance performance (*M*=72.48, *SD*=64.42) during the CPT. Placebo analgesia, on average, was larger on pain-threshold performance (*M*=13.72, *SD*=13.51) compared to control performance (*M*=10.06, *SD*=14.11) on the CPT. However, on average, placebo analgesia had no effect on pain-tolerance performance (*M*=78.72, *SD*=60.93) compared to control performance (*M*=72.48, *SD*=64.42) on the CPT.

Descriptive Statistics

PAIN SCORES	Mean	Std. Deviation
Hypnosis Analgesia Pain-Threshold	78.83	71.697
Placebo Analgesia Pain-Threshold	13.72	13.518
Control Pain-Threshold	10.06	14.115
Hypnosis Analgesia Pain-Tolerance	111.07	66.736
Placebo Analgesia Pain-Tolerance	78.72	60.938
Control Pain-Tolerance	72.48	64.427

Table 1: Paired-samples *t*-test which shows the Mean and Std. Deviation for the Pain- Threshold and Pain-Tolerance Scores on the Cold Pressor Task, between Hypnosis Analgesia, Placebo Analgesia and Control, as measured in seconds.

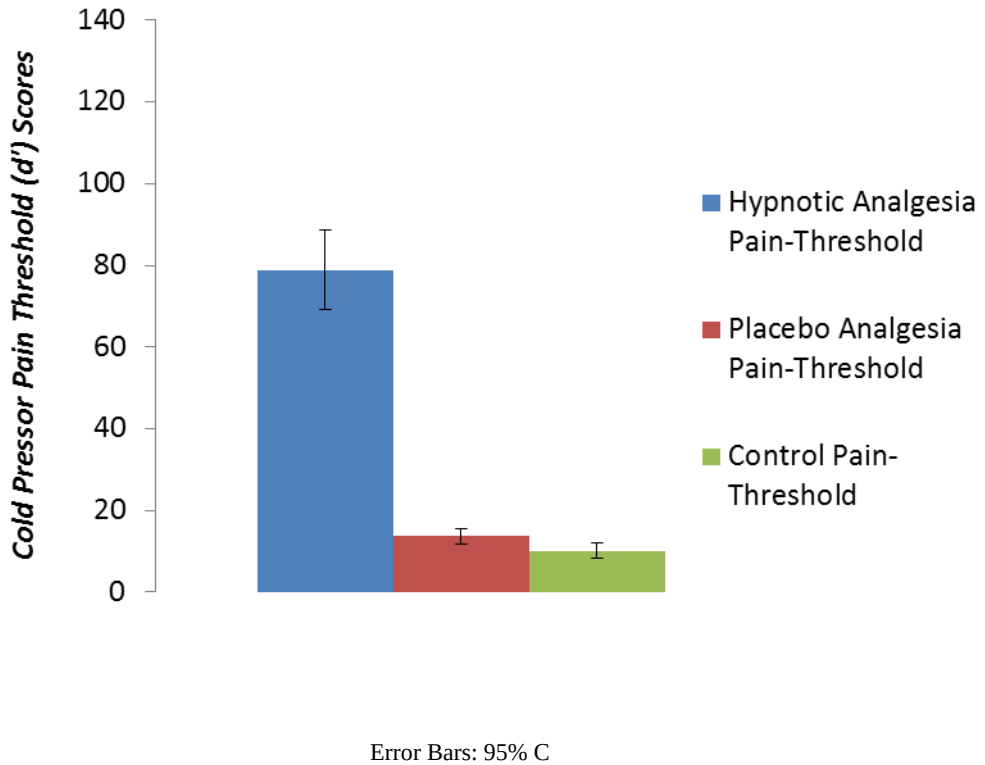

Figure 3: Mean (d') scores for the Cold Pressor Pain Threshold Scores (Seconds)

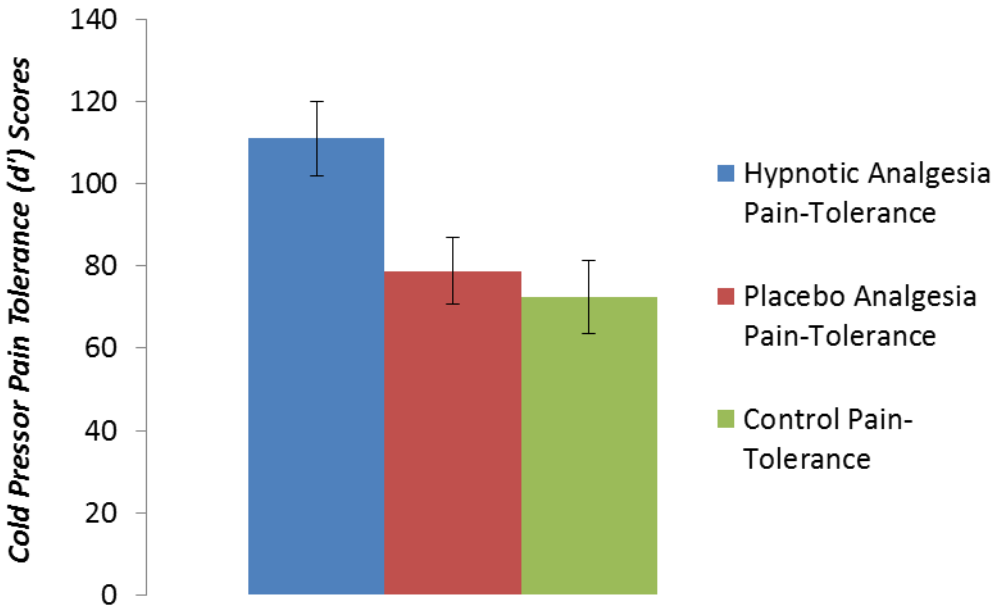

Figure 4: Mean (d') scores for the Cold Pressor Pain-Tolerance Scores (seconds)

Pain-Threshold in relation to Hypnotic Analgesia, Placebo Analgesia and Control

Tests of Normality indicate that there may be some inconsistency in the normal distribution of pain-onset scores. ANOVA's are robust to violations of normality; however, results should be interpreted with caution. A repeated-measures one-way ANOVA was computed with Treatment (Hypnotic analgesia, placebo analgesia and control) as the independent variable and pain threshold scores as the dependent variable. There was a significant main effect of treatment [$F(1.014, 53.76) = 46.790$, $p = .001$, $\eta_p^2 = .469$].

To explore the effect further between pain scores, three separate paired-samples t-tests concerning pain-threshold were computed between hypnotic analgesia, placebo analgesia and control. When comparing pain-threshold levels in the hypnotic analgesia condition against the control condition; $t(53 = 6.998$, p= .001 (one-tailed), (hypnosis analgesia, $M = 78.83$, $SD = 71.70$; control, $M = 10.06$, $SD = 14.12$), the effect size was very large ($d = 1.33$). Concerning pain-threshold levels for placebo analgesia versus control, there was also a significant difference $t(53 = 3.829$, p= .001 (one-tailed), (placebo analgesia, $M = 13.72$, $SD = 13.52$; control, $M = 10.06$, SD = 14.12) although the effect size was very small ($d = 0.27$). Interestingly, there was a

significant difference for pain-threshold levels concerning hypnosis analgesia against placebo analgesia, *t*(53= -6.699, p= .001 (one-tailed), (hypnosis analgesia, *M* = 78.83, *SD* = 71.70; placebo analgesia, *M* = 13.72, *SD* = 13.52), the effect size was very large (*d* = 1.26).

Pain-Tolerance in relation to Hypnotic Analgesia, Placebo Analgesia and Control

Tests of Normality indicate that there may be some inconsistency in the normal distribution of pain-onset scores. ANOVA's are robust to violations of normality; however, results should be interpreted with caution. A repeated-measures one-way ANOVA was computed with Treatment (Hypnotic analgesia, placebo analgesia and control) as the independent variable and pain-tolerance scores as the dependent variable. There was a significant main effect of treatment [*F*(1.374, 72.81) = 18.900, *p* = .001, η_p^2= .263].

To explore the effect further between pain scores, three separate paired-samples t-tests concerning pain-tolerance were computed between hypnotic analgesia, placebo analgesia and control. When comparing pain-tolerance levels in the hypnotic analgesia condition against the control condition; *t*(53= -4.750, p= .001 (one-tailed), (hypnosis analgesia, *M* = 111.07, *SD* = 66.74; control, *M* = 72.48, *SD* = 64.43), the effect size was medium (*d* = 0.59). There was however a surprising non-significant effect for placebo analgesia versus control, concerning pain-tolerance levels, *t*(53= 1.588, p= .118 (one-tailed), (placebo analgesia, *M* =78.72, *SD* = 60.94; control, *M* =72.48, *SD* = 64.43). Concerning pain-tolerance levels between hypnosis analgesia versus placebo analgesia there was a significant difference, *t*(53= -4.371, p= .001 (one-tailed), (hypnosis analgesia, *M* = 111.07, *SD* = 66.74; placebo analgesia, *M* = 78.72, *SD* = 60.94) the effect size was medium (*d* = 0.51).

Predictors of Hypnosis Analgesia Pain-Threshold

A three-stage hierarchical multiple regression was chosen since, as noted in the introduction, it was reasoned that the Paper Stroop task would be a stronger predictor of hypnotic analgesia than either the Hayling or fluid IQ scores. Multicollinearity was checked and found to be within the acceptable limit. The Paper Stroop task was entered at stage one of the regression to predict the magnitude of hypnotic analgesia threshold performance during the Cold Pressor Test and was non-significant, *F*(1, 52) = .018,

$p < .893$) and accounted for 0% (Adjusted $R^2 = 1.9\%$) of the variance in performance. The Hayling Sentence Completion task entered at stage two was also non-significant $F(2, 51) = .009$, $p < .991$) and accounted for 0% (Adjusted $R^2 = -.039$) of the variance in performance. Fluid IQ was entered at stage three and was also non-significant $F(3, 50) = .010$, $p < .999$) and accounted for 0% (Adjusted $R^2 = -.059$) of the variance in performance. The EF tasks were entered in this order based on a priori predictive value outlined in the introduction. At no stage was there a predictive relationship between EF and hypnotic analgesia pain-threshold.

Table 2 gives information for the predictor variables that are included in the model. The pathways from each predictor variable to the pain scores outcome variable quantify the strength of these relationships, in terms of standardised regression weights. As an example, the β weight of .01 indicates that a 1 SD increase in hypnotic analgesia corresponds to an increase of .01 SD in decreased pain sensitivity during the Cold Pressor Test.

Variable	**B**	**SE B**	**β**
Step 1			
The Paper Stroop Task	-0.19	1.42	-.02
Step 2			
The Paper Stroop Task	-0.19	1.44	-.02
The Hayling Sentence Completion Task	0.37	12.12	.00
Step 3			
The Paper Stroop Task	-0.19	1.45	-.02
The Hayling Sentence Completion Task	0.62	12.50	.01
Fluid IQ	-0.08	0.75	-.02

Table 2: Summary of Hierarchical Regression Analysis for Variables predicting hypnosis analgesia pain-threshold

Predictors of Placebo Analgesia Pain-Threshold

A three-stage hierarchical multiple regression was chosen since, as noted in the introduction, it was reasoned the Hayling task would be a stronger predictor of placebo analgesia than either the Paper Stroop Task or fluid IQ scores. Multicollinearity was

checked and found to be within the acceptable limit. The Hayling Sentence Completion task, which was entered at stage one of the regression to predict the magnitude of placebo analgesia pain-threshold performance, during the Cold Pressor Test, almost contributed significantly to the regression model, $F(1, 52) = 3.738$, $p < .059$) and accounted for 0% (Adjusted $R^2 = .049$) of the variance in performance. At stage 2 however, when IQ was added and controlled for, the Hayling became significant, $F(2, 51) = 3.963$, $p > .025$) and explained an additional 13.5% (Adjusted $R^2 = .101$) of variation in threshold performance, while IQ was almost significant as a predictor of placebo analgesia, $p < .052$. Finally, when the Stroop Task was entered at stage three to the model and controlled for, the Hayling Task further contributed to model significantly, $F(3, 50) = 2.799$, $p > .049$) and explained an additional 14.4% (Adjusted $R^2 = .092$) of variation in threshold performance. While the Paper Stroop Task was not significant to the model, $p < .465$, Fluid IQ was at levels of significance, $p < .051$, which is a good predictor of placebo analgesia threshold. The EF tasks were entered in to this order based on a priori predictive value outlined in the introduction.

Table 3 gives information for the predictor variables included in the model.

Variable	**B**	**SE B**	**β**
Step 1			
The Hayling Sentence Completion Task	-2.18	1.13	-.26
Step 2			
The Hayling Sentence Completion Task	-2.61	1.12	-.31*
Fluid IQ	0.13	0.08	.27
Step 3			
The Hayling Sentence Completion Task	-2.58	1.12	-.31*
Fluid IQ	0.14	0.07	.28*
The Paper Stroop Task	0.10	0.13	.10

*p < .05

Table 3: Summary of Hierarchical Regression Analysis for Variables predicting placebo analgesia pain-threshold.

Predictors of Hypnotic Analgesia Pain-Tolerance

A three-stage hierarchical multiple regression was chosen on the same basis as the threshold analysis. Multicollinearity was checked and found to be within the acceptable limit. The Paper Stroop Task, which was entered at stage one of the regression, to predict magnitude of hypnotic analgesia tolerance performance, during the Cold Pressor Test was non-significant to the model, $F(1, 52) = .129$, $p < .721$) and accounted for 0% (Adjusted $R^2 = -1.7$) of the variance in performance. The Hayling Sentence Completion task was entered at stage two of the model was also non-significant $F(2, 51) = .424$, $p < .657$) and accounted for 0% (Adjusted $R^2 = -2.2$) of the variance in performance. Additionally, Fluid IQ entered at stage three of the model was also non-significant $F(3, 50) = .338$, $p < .798$) and accounted for 0% (Adjusted $R^2 = -.39$) of the variance in performance. The EF tasks were entered in to this order based on a priori predictive value outlined in the introduction. At no stage was there a predictive relationship between EF and hypnotic analgesia pain-tolerance.

Table 4 gives information for the predictor variables included in the model.

Variable	**B**	**SE B**	**β**
Step 1			
The Paper Stroop Task	0.42	1.18	.05
Step 2			
The Paper Stroop Task	0.38	1.20	.05
The Hayling Sentence Completion Task	-8.43	9.94	-.12
Step 3			
The Paper Stroop Task	0.37	1.20	.04
The Hayling Sentence Completion Task	-7.60	10.21	- .11
Fluid IQ	-0.26	0.62	-.06

Table 4: Summary of Hierarchical Regression Analysis for Variables predicting hypnosis analgesia pain-tolerance.

Predictors of Placebo Analgesia Pain-Tolerance

A three-stage hierarchical multiple regression was chosen on the same basis as the threshold analysis. Multicollinearity was checked and found to be within the acceptable limit. Overall, the 3-stage model was not a predictor of placebo analgesia tolerance, during the Cold Pressor Test: The Hayling Sentence Completion task was entered at stage one of the regression and was non-significant, $F(1, 52) = 3.144$, $p < .070$) and accounted for 0% (Adjusted $R^2 = .044$) of the variance in performance. At stage 2, when Fluid IQ was entered, the model was again non-significant, $F(2, 51) = 2.792$, $p < .071$) and accounted for 0% (Adjusted $R^2 = .063$) of the variance in performance. However, once IQ was entered and controlled for, the Hayling became a significant predictor of placebo analgesia tolerance at stage 2, p< .040, suggesting that IQ modifies the relationship between placebo analgesia and performance on the Hayling task. When the Paper Stroop task was added the model was still non-significant, $F(3, 50) = 2.301$, $p < .088$) and accounted for 0% (Adjusted $R^2 = .069$) of the variance in performance. Performance on the Hayling task was still a significant predictor at this stage 3, p< .043.

Table 5 gives information for the predictor variables included in the model.

Variable	**B**	**SE B**	**β**
Step 1			
The Hayling Sentence Completion Task	-8.60	4.65	-.25
Step 2			
The Hayling Sentence Completion Task	-9.90	4.70	-.29*
Fluid IQ	0.41	0.28	.20
Step 3			
The Hayling Sentence Completion Task	-9.71	4.68	-.28*
Fluid IQ	0.42	0.28	.20
The Paper Stroop Task	0.62	0.55	.15

*p < .05

Table 5: Summary of Hierarchical Regression Analysis for Variables predicting placebo analgesia pain-tolerance.

4. Discussion

Prominent researchers have reported that hypnosis and placebo are associated through suggestion, consequently links have been drawn between the two phenomena (Raz, 2007; Kirsch, 1997). In contrast, other researchers have indicated a dissociation between hypnosis and placebo, suggesting that they may have a different reliance on PFC function (e.g. Landry et al., 2017; Parris, 2016b). Consequently, the present study looked to investigate the differences and similarities between hypnosis and placebo using pain-analgesia scores on the CPT (Rash & Campbell, 2004).

This study found a large effect of hypnotic analgesia on pain-threshold performance during the CPT. In fact, hypnotic analgesia was greater in magnitude than both placebo analgesia and control condition. Additionally, hypnotic analgesia pain-tolerance was greater in magnitude than placebo analgesia, revealing a medium effect size. There was also a significant effect of placebo analgesia on pain-threshold performance compared to control on the CPT, although the effect size was marginal. However, placebo analgesia was not significant on pain-tolerance performance.

4.1 Differences between Hypnotic and Placebo Analgesia

The difference between the placebo and hypnotic analgesia performance maybe due to several factors. Firstly, literature has reported that hypnosis is more powerful at reducing pain sensation than placebo (McGlashan et al., 1969; Milling et al., 2005). Secondly, Hull (1993) reported that placebo is produced via indirect suggestions (false statements inducing gullibility) and hypnosis is produced via direct suggestions (imaginative), and it is worth considering that direct suggestions may be more powerful. Thirdly, Placebo suggestibility has been found to be less stable than hypnosis (Piccione, Hilgard, & Zimbardo, 1989). As such, placebo responses have been reported as being inconsistent, unreliable and tenuous, due to the involvement of complex interactions between context (e.g. situational variable and expectations), environmental cues, individual traits (Darragh, Booth & Considine, 2015; Horing, Weimer, Colloca & Enck, 2015), and the pharmaceutical properties suggested (Whalley, Hyland & Kirsch, 2008) affecting research outcomes (Lifshitz, Sheiner, Olson, Theriault & Raz, 2017). For example, Darragh, Booth & Consedine (2015) have suggested that greater placebo responding can occur if an individual's orientation

is matched to the nature of contextual cues, environmental variables and contingencies. Thus, individuals fall in to one of two orientations; either an "inward/approach" orientation belonging to an individual who is internally focused, sensitive to signals of punishment and anxiety or an "outward/avoid" orientation, belonging to an extraverted individual who is optimistic and responds to novelty, goals and reward (Darragh et al., 2015). Interestingly, Evans (1974), reported that changing the pharmaceutical properties of suggested placebo can enhance the placebo effect. For example, administering placebo morphine is more effective than administering a Darvon Placebo pill (Evans, 1974); as such, individuals would have expected Morphine to deliver a stronger physiological result. Consequently, the present research may have benefited from administering each participant with a placebo pill or placebo morphine to strengthen the placebo effect, instead of using the 'Travaricane' placebo-analgesia cream.

A fourth possible factor for the significant performance of hypnosis analgesia over placebo analgesia was that in the present study, after hypnotic induction, participants continued to receive suggestions for pain reduction and relaxation during the CPT, and this would have motivated them to keep their hand immersed for longer. If, in the present study, participants who were undertaking the placebo analgesia condition had repeated suggestions during the CPT, adapted from the suggestions given in the hypnotic analgesia condition (for example, 'Travaricane is proven too much reduce pain sensation, therefore your hand is insensitive to pain and no pain sensation will occur…,' (Casiglia et al., 2007; Montgomery & Kirsch, 1996), then there may have been a greater placebo effect. For example, when Milling et al. (2005) conducted non-hypnotic, imaginative pain-analgesia suggestion, without mentioning hypnosis or conducting a hypnotic induction, they found it to be as effective as standard hypnosis. Additionally, when Accardi et al. (2013, p108) told participants in a placebo-hypnosis condition that "hypnosis is actually a placebo" but without deception, their responses were highly comparable to participants in a standard-rational hypnosis condition. In a sense then, a combination of placebo with non-hypnotic, imaginative pain-analgesia suggestion may have certainly increased placebo responding.

A fifth possible factor influencing the performance variation between placebo and hypnotic analgesia may have been to do with the long-standing belief that people have about hypnosis being an altered state phenomenon. Therefore, the participants in the present study may have consciously or unconsciously believed that the hypnotist conducting the research was 'altering their state' in some way (Nash & Barnier, 2008), thus reducing, in participants' minds, any parallels between the hypnosis and placebo condition being a related phenomenon.

A sixth possible factor influencing the performance variation between placebo and hypnotic analgesia could have been affected by ceiling effects. It may be that 180 seconds is not long enough because the spread of this study's scores had a very close spread at 180 seconds' duration. Although this study followed previous CPT research (von Baeyer et al., 2005) using a duration of 180 seconds, von Baeyer et al. also informed that 240 seconds can be used for each CP immersion to avoid ceiling effects. However, von Baeyer et al. also suggested using an 'Informed Ceiling Task', rather than using timed tolerance. Participants are asked to keep their hand submersed for 60 seconds only and then complete a pain rating scale: which may provide greater standardisation of cold immersion and greater variability than tolerance timings. Therefore, a replication of this study would benefit from using the informed ceiling task instead.

A last possible factor influencing the performance variation between placebo and hypnosis, although a small factor, could be due to the fact that the advertisement placed within the University Campus only mentioned 'Hypnosis and Pain Perception.' This may have made participants more suggestible and expectant to the efficacy of hypnosis over placebo. However, when students and staff responded to the advertisement they were told quite specifically that the study would be comparing hypnotic analgesia against a pain-analgesia cream and also against a control, and this should have equally balanced suggestibility and expectation towards hypnosis and pain-analgesia cream (placebo).

4.2 EF Tasks as Predictors for Hypnotic and Placebo Analgesia Pain-Threshold and Pain-Tolerance:

This study investigated whether placebo and hypnotic analgesia were reliant on PFC. Moreover, the present research aimed to ascertain whether there was an effect of hemispheric laterality on the experience of either forms of analgesia. It was expected that the Hayling Sentence Completion task (a right frontal, dominant task) would predict the magnitude of placebo analgesia, while the Paper Stroop Task (a left frontal, dominant task) would predict the magnitude of hypnotic analgesia. Additionally, Fluid IQ was investigated as an additional predictor variable towards global PFC reliance, in a further attempt to investigate similarities and differences between the two types of suggestion.

4.2.1 Hypnosis Analgesia Pain-Threshold and Pain-Tolerance

The EF predictor variables of the Paper Stroop Task, the Hayling Sentence Completion Task and Fluid IQ scores did not significantly predict the magnitude of hypnotic analgesia pain-threshold or pain-tolerance performance. This was unexpected as Cipolotti et al's. (2016) research reported that the Stroop Task, which is an inhibitory task, corresponded with left PFC functioning. Other research has also indicated evidence for left hemisphere functioning during hypnosis (e.g.; Egner, Jamieson & Gruzelier, 2005; Laria et al., 2008; Kosslyn et al., 2000), including Dienes and Hutton (2013), who found, in support of CCT (Dienes & Perner, 2007), that rTMS stimulation to the left DLPFC increased hypnosis by 6% (due to inhibition within the PFC). However, this study's findings have found it hard to support CCT (Dienes & Perner, 2007), which predicts that inhibition of the left PFC is required for successful hypnotic suggestibility to occur (Dienes & Hutton, 2013), as this study found no such relationship.

In contrast, Terhune et al. (2011), in line with DCT (Woody & Bowers, 1994), found support for a decrease in global PFC and reduced cognitive control (connectivity) during hypnosis in HHIs, who scored highly on the Dissociative Experiences Scale (DES; having certain experiences of clinical dissociation in their everyday life; Bernstein & Putnam, 1986). Additionally, Gruzelier (2014), found that during hypnosis HHI activated the left hemisphere first (including the DLPFC) and

then switched to the right hemisphere, when they experienced the 'letting go' process during hypnosis. Consequently, it was surprising that the present research also found no relationship with hypnotic analgesia and the right hemisphere via the Hayling Task either (Cipolotti et al. reported that the Hayling, also an inhibitory task, corresponded with right PFC functioning), or with Fluid IQ, a global PFC task. Thus, this study's finding can also not confirm DCT (Woody & Bowers, 1994), which advocates that inhibition to the left and right PFC is required for successful hypnotic suggestibility to occur.

However, Parris (2016b) reported in his review that research relating to hypnotic functioning within the brain was mixed and that at present no clear conclusion could be drawn. Interestingly, the present study could also not draw a conclusion relating PFC function and hypnotic analgesia, since none of the measures of PFC functions significantly predicted hypnotic analgesia. Previous researchers have also found it hard to specify the exact mechanisms of the brain responsible for the difference between HHIs and LHIs. For example, there has been contradictory findings that HHIs and LHIs have no differences at baseline or during hypnosis on tasks that are thought to index frontal lobe function (e.g. the Stroop task; Stroop, 1935) (Dienes et al., 2009; Varga et al., 2011). Yet, Blum and Graef (1971), Dixon et al. (1990), Dixon and Laurence, (1992), Farvolden and Woody (2004) and Lynn and Green (2011) have reported that HHIs have been found to exhibit weakened frontal control and greater Stroop conflict than LHIs, both at baseline and under hypnosis. Parris (2016a) attributes that the difference in findings may be due to the researchers' methodology, using tasks which may not clearly involve the DLPFC or failing to titrate task difficulty.

Moreover, a current review and meta-analysis by Landry et al., (2017) also reported that the large variation in hypnotic methodological standards, coupled with the complex nature of hypnosis, has made it difficult to generalize which mechanisms are specifically associated with hypnosis. Through their fMRI study, Landry et al. proposed that it was the lingual gyrus (a left hemisphere function, not within the PFC, but at the back of the head, in the occipital lobe), that may actually play the crucial role in hypnotic responding, due to it enhancing hypnotic mental imagery. The lingual gyrus is related to imagination, which is a fundamental attribute of HHI; consequently

there may be some validity in Landry et al's. research. Thus, the neural substrate for hypnotic analgesia is potentially more posterior than anterior.

4.2.2 Placebo Analgesia Pain-Threshold and Pain-Tolerance

The Hayling Sentence Completion Test as a predictor of the magnitude of Placebo analgesic pain-threshold performance, on its own, was not significant. However, when Fluid IQ was entered at stage two of the model, the Hayling became a significant predictor of the magnitude of Placebo Analgesia pain-threshold performance, while Fluid IQ, at stage 2 was almost a significant predictor. At stage 3, when the Paper Stroop was added, the Hayling significance was reduced marginally, and Fluid IQ then showed a level of significance.

In contrast to Krummenacher et al., (2010) and Wager et al., (2004), who found a bilateral effect for placebo, the present results, in line with Egorova et al., (2015), Graff-Guerrero et al. (2005), Leuchter et al. (2002), Lieberman et al. (2004), Pariente et al. (2005) and Wager & Atlas (2015), show that placebo analgesia is reliant on the right PFC, as predicted by the Hayling task, during pain-threshold and pain-tolerance performance; and importantly supports Cipolotti et al's. (2016) findings that the Hayling task is a predictor of right PFC inhibition. The findings also support current literature which strongly indicates that normal or increased functioning of the PFC is required for the placebo effect to take place (Benedetti, 2010).

Fluid IQ was also a significant predictor of pain threshold, although interestingly it was not related to pain-tolerance. This suggests that there is a relationship happening between global PFC and the right PFC that enhanced the time from the point of submersion to pain threshold, but not between placebo pain-threshold and placebo pain-tolerance. A further possible explanation for the relationship between global Fluid IQ and the right PFC may be due to the multiple demand network (MDN; a large PFC parietal network, linked with an array of cognitive process identified during functional imaging tasks, e.g. Woolgar et al., 2010) within the brain. Through functional imaging of 80 patients with cerebral focal lesions, Woolgar et al. (2010) proposed that Fluid IQ may involve different neural substrates within the MDN, that contribute differently to cognitive control functions (MacDonald, Cohen, Stenger & Carter, 2000; Dosenbach et al., 2006). Accordingly, if the MDN is made up of

different neural substrates (the lateral prefrontal cortex (LPFC), aspects of the inferior frontal sulcus (IFS) and the anterior frontal cortex (AFC), the anterior insula/frontal operculum (AI/FO), the dorsal anterior cingulate/pre-supplementary motor area (ACC/pre-SMA), and the intraparietal sulcus (IPS)), then these neural substrates might of had an independent effect on placebo analgesia and effectively tapped regions of the right PFC, that the Hayling did not, thus increasing Fluid IQ's predictive power (Woolgar et al., 2010). Consequently, this would support Cipolotti et al., who also found that the Hayling task was not entirely mediated by Fluid IQ. Woolgar et al. (2010) also found that different neural substrates of the MDN showed a reduction in IQ where a lesion was associated (e.g. $10cm^3$ frontal MD damage = 6.4 fewer IQ points). Accordingly, if each substrate of the MDN contributes to Fluid IQ (Woolgar et al., 2010), and the present research found that fluid IQ positively modified the relationship between the Hayling and placebo analgesia, then this may suggest that individuals with greater Fluid IQ scores may experience greater placebo analgesia. Hence, it may benefit pharmaceutical companies, when undertaking clinical trials, to administer a Fluid IQ test to each participant, in order to identify and exclude GPRs from the trial, as their results potentially mask the significant effect of the drug being tested (Raz, 2005).

While the present study did not find any overall similarity between the phenomena of placebo or hypnotic suggestibility, it is worth considering that this study may have been underpowered, as there were only 54 participants (and three predictors). Although a rule of thumb is to have 10 x the number of predictors (Field, 2009), Green (1991) suggests that a study should have eight participants for every predictor, plus 50. Therefore, the present study would have benefited from a sample size of 74 participants to test the model overall.

4.3 Conclusion

In conclusion, prominent theoreticians have referred to hypnosis as a mega placebo (Kirsch, 1997) or "hypnobo" (Raz, 2007), suggesting that hypnosis and placebo are effectively the same phenomenon. However, there has also been evidence that their mechanisms of action are different (Parris, 2016a). Placebo effects have been found to rely on the right prefrontal cortex (PFC; Benedetti, 2010), while the role of the PFC in

hypnosis and hypnotic suggestibility has been inconclusive (Parris, 2016b). Consequently, the present study asked participants to perform tasks known to tap either left (the Stroop Task), right (the Hayling Task) or global PFC functions (Fluid IQ; SHSC: Form C), based on Cipolotti et al's. (2016) work, and were then given both hypnotic and placebo analgesia prior to completing the Cold Pressor Test. Overall, hypnotic suggestibility vastly determined the magnitude of reduction in pain sensitivity, in relation to both the pain-threshold and pain-tolerance performance, compared to placebo analgesia and the control condition. Surprisingly, placebo analgesia was non-significant over the control condition concerning pain-tolerance performance, and only had a marginal effect over pain-threshold performance. Other research in line with the present study, has also found placebo analgesia to be less powerful than hypnotic analgesia (McGlashan et al., 1969; Milling et al., 2005). Placebo has also reportedly been found to be less stable than hypnosis (Darragh, Booth & Considine, 2015; Horing, Weimer, Colloca & Enck, 2015). In line with Krummenacher et al., the present study's results showed that placebo analgesia was related to right PFC and global PFC functioning. However, this study also found that Fluid IQ (as a predictor of global PFC functioning) appears to positively modify the relationship between the Hayling Task, the right prefrontal cortex and placebo analgesic pain-threshold. This may suggest that individuals with greater Fluid IQ scores may experience greater placebo analgesia. Thus, it may benefit pharmaceutical companies, when undertaking clinical trials, to administer a Fluid IQ test to each participant in order to identify and exclude GPRs from the trial, as their results potentially mask the significant effect of the drug being tested (Raz, 2005).

Interestingly, the present study also found that hypnotic analgesia was not related to performance on any PFC task, nor did it find an overall similarity between the two phenomena in terms of PFC functioning. Thus, it may be that hypnotic functioning may involve the lingual gyrus, as Landry et al. (2017) proposed. Overall, the present study's results imply that clinical pain can be treated successfully by hypnotic suggestion. Thus, participants with frontal atrophy of the PFC, having lost the ability to experience the placebo effect through stroke or dementia (Benedetti et al., 2006), would benefit from hypnotic analgesia instead.

Therefore, further research is still needed to compare and contrast the role of FEFs in hypnotic and placebo responding (Parris, 2016a; Parris, 2016b). Future research would benefit from replicating this study and incorporating Darragh et al's. approach to increasing the stability of placebo responding. Additionally, using a larger sample size and administering each participant with a placebo pill or placebo morphine, with an aim to strengthen the placebo effect, would be beneficial. It would also be interesting to add a fourth condition to the study, where participants undertaking placebo analgesia would receive non-hypnotic suggestions during the CPT. Additionally, changing the CPT tolerance timing from 180 seconds to 280 seconds would increase the spread and variation of participant data across pain tolerance timings and help remove any potential ceiling effects; or use an informed ceiling test to provide greater standardisation (von Baeyer et al., 2005), as ceiling effects may have affected this study's overall outcome. Thus, replicating this study will answer questions that will help to determine the efficacy of placebo responding and to help ascertain more clearly the hemispheric region of hypnotic responding.

However, what this study has found is that hypnotic suggestion was significantly more effective at analgesic pain-threshold and tolerance than placebo suggestion, and that Fluid IQ, as a predictor of global prefrontal cortex functioning, appears to positively modify the relationship between the Hayling Task, the right prefrontal cortex and placebo analgesic pain-threshold.

5. References

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6. Appendices

6.1 Appendix A: Participant Information Sheet

Using hypnotic suggestion to improve performance on a hand immersion task

You are being invited to take part in a research project. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Please ask us if there is anything that is not clear, or if you would like more information. Take time to decide if you wish to take part.

What is the purpose of the project?

The aim of this project is to ascertain whether hypnotic suggestion can be used to improve performance on a task that requires you to immerse your hands, alternately, in very cold water (The Cold Pressor Test). Recent research suggests that hypnotic suggestion can be very powerful and consequently, it is currently used in medical settings. The effect of the hypnotic suggestion will be compared to a medical analgesia hand-cream, proven to reduce the sensation of discomfort and pain. Additionally, we will be looking to see if susceptibility to hypnotic suggestion is determined by left or right frontal lobe function (frontal area in the brain partly responsible for executive function e.g. reasoning, planning & multi-tasking etc.).

Why have I been invited?

The study aims to recruit up to 50 participants from the Poole and Bournemouth area, and from Bournemouth University's student population.

Do I have to take part?

It is entirely up to you to decide if you wish to participate or not. If you do decide to take part, you will be given this information sheet to keep. You will also be asked to sign a consent form to show that you agree to take part. You are free to withdraw from this study at any point in time (and any data collected will be removed, up until the point of anonymisation), without giving a reason.

What do I have to do?/ what will happen to me if I take part?

You will then be asked to complete 3 executive function tasks (approximately 5-15mins each) that require you to respond as quickly and as accurately as you can to the font-colours of words presented on paper (a task known as the Stroop Task, a left frontal dominant task). Secondly: to complete sentences using words that are not related to the sentence topic (the Hayling Sentence Completion Task, a right frontal dominant task). Thirdly: using reason and logic twice, solve novel problems, identify

patterns and relationships within these problems (Fluid Intelligence Tasks, also a measure of frontal lobe function).

IN A COUNTERBALANCED ORDER: you will then have hand-cream applied to either your dominant or non-dominant hand, before being asked to immerse your hand in to a small tank of ice-cold water (Cold Pressor Task (CPT)). You will remove it when, due to discomfort, you cannot keep it there any longer (maximum 180 seconds). After you have chosen to remove your hand, you will then be able to warm it against a hot water bottle for 2minutes. You will then have hand-cream applied for a second time on your alternate hand and repeat the CPT, removing it when you feel cold discomfort, and again warming it against a hot water bottle, for 2minutes. The third and final CPT will be undertaken again on your alternate hand, as above. We will be measuring your heart rate and blood pressure, before (to get a baseline reading) and during the CPT (not because we think the task is of any risk to you, but instead will allow us to eliminate heart rate/blood pressure factors later, as being related to the length of time you could keep you hand in the water).

COUNTERBALANCING: hand-cream application 1, will be a medical analgesia hand-cream to help you perform well on the CPT; hand-cream application 2, will be a control hand-cream (hand-cleanser cream); hand-cream application 3 will also be a hand-cleanser cream, however, prior to submersing your hand in the CPT you will be hypnotised using a very short hypnotic induction, ideal for the CPT, and then given a hypnotic suggestion to help you perform well on the CPT (to compare the effect of hypnotic analgesia, against the other two conditions).

The executive functions tasks and questionnaires will take 30-45mins, the Cold Pressor Task, including hypnosis will take 45mins -1hr. You will receive credit for your time.

This research is being undertaken by Dr. Ben Parris, a Cognitive Neuroscientist at Bournemouth University and his research assistants. The experimental task is entirely safe and has been used many times before; there is a large literature on the CPT and hypnosis.

What are the possible disadvantages and risks of taking part?

The British Psychological Society have stated that taking part in research involving hypnosis has no risks or disadvantages greater than that associated with any psychological experiment. However, since the experiment could take up to 1.45hrs, you may feel a little fatigued at the end of the experiment.

Given that the study is about pain perception, you will experience mild to moderate cold pain during the CPT. Importantly, you will be completely in control over how much discomfort you feel, as you can choose when to remove your hand from the CPT. Since we are using cold water that is initially not painful to the touch, there is no

chance of any dermatological damage; your hand will of course be redder upon retraction, but this will return to normal after a short period.

What are the possible benefits of taking part?

Whilst there are no immediate benefits for participating in the project, this research is exploring the possible use of hypnosis as a powerful tool in self-control. This research will add to the growing literature on the use of hypnosis in neuroscience research. It is hoped that this work will contribute to our understanding of the clinical and medical uses of hypnosis in pain reduction, and will be of tremendous benefit for those suffering from chronic or acute pain. You may also find participating interesting.

Will my taking part in this project be kept confidential?/What will happen to the results of the research project?

All the information that we collect about you during the research will be stored securely and kept strictly confidential. Only the researchers will have access to this data. You will be given a research code known only by the researchers, so that you will be unidentifiable in any reports or publications. We will aim to publish the data in an international peer-reviewed journal and will keep the data for no longer than 5 years after the completion of the study, after which it will be destroyed/deleted.

What type of information will be sought from me and why is the collection of this information relevant for achieving the research project's objectives?

We will be collecting various types of information from you: 1) performance scores on the Stroop Task and Hayling Task to see if they are related to your susceptibility to hypnotic suggestion and determined by left or right frontal lobe function; 2) The two Fluid Intelligence' Tasks, which are also a measure of general frontal lobe function, but not related to the above two tasks, and will be used to match participant's ages and ability evenly; 3) How long before you begin to feel discomfort (Pain-threshold) during the CPT, and how long you can keep your hand submersed in the very cold water (Pain-tolerance); 4) Heart rate and blood pressure readings, so that we can remove these as factors contributing to pain threshold and pain tolerance in later analysis.

Who is organising/funding the research? (If applicable)

This research is being run by Dr. Ben Parris, Principle Lecturer and Head of Research in the Psychology Department, within the Faculty of Science and Technology; and is funded by the Department.

Who has reviewed the project?

This study has been review by Bournemouth University's Ethical Approval Committee.

Contact for further information

For further information please contact Dr Ben Parris on bparris@bournemouth.ac.uk or 01202 965485. You could also visit Dr Parris' office on the third floor of Poole House in room P331 on Wednesday afternoons between 2pm and 5pm.

If you wish to make a complaint about any aspect of the study, you should contact Professor Christine Maggs, who is Dean of the Faculty of Science and Technology at Bournemouth University. Christine's contact details are as follows; Address:

Faculty of Science and Technology, Bournemouth University, Talbot Campus, Fern Barrow, Poole. Dorset. BH12 5BB. Telephone: 01202 965847. E-mail: researchgovernance@bournemouth.ac.uk

Thank you for taking the time to read through the information. Please take this information sheet with you when you leave.

6.2 Appendix B: Participant Details Form

Participant Details Form

Participant code: _____

Bournemouth University

General Details

First Name: _____ Surname: _____

Age: _____ Gender: _____

First language: _____

If you are not British, please rate your fluency in English below:

(Very Poor) 1 2 3 4 5 *(Excellent)*

Dominant Writing Hand: _____

Have you used the Cold Pressor Task before?	Yes / No
Do you have a heart condition?	Yes / No
Do you take any medication for your heart?	Yes / No
Do you suffer with a pain condition?	Yes / No
Do you take any medication for your pain?	Yes / No
Have you been hypnotised before?	Yes / No
Are you on anti-depressants/antipsychotic medication?	Yes / No
Do you suffer with Epilepsy?	Yes / No
Have you had a stroke?	Yes / No
Do you have a feeling of pain anywhere today?	Yes / No

Contact Details

Email Address: _____

Telephone (Optional): _____

Signature: _____ **Date**: _____

6.3 Appendix C: Participant Consent Form

CONSENT FORM

Hypnosis, Frontal Lobe and Pain Perception

Dr. Ben Parris, Principle Lecturer and Head of Research in Psychology:

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Please Initial Here

I confirm that I have read and understood the participant information sheet for the above research project and have had the opportunity to ask questions.	
I understand that my participation is voluntary and that I am free to withdraw until the results are anonymised, without giving reason and without there being any negative consequences. In addition, should I not wish to answer any particular question(s) or complete a test, I am free to decline.	
I give permission for members of the research team to have access to my anonymised responses. I understand that my name will not be linked with the research materials, and I will not be identified or identifiable in the report or reports that result from the research.	
I agree to take part in the above research project.	

Name of Participant Date Signature

_____ _____ _____

Name of Researcher Date Signature

_____ _____ _____

Name of Researcher Date Signature

_____ _____ _____

6.4 Appendix D: Oxford Induction Procedure for CPT

OXFORD INDUCTION PROCEDURE FOR CPT:

(Remind participants that hypnosis is a very powerful tool, as it is used on cancer patients to dramatically reduce pain and in surgeries and dentistry replacing anaesthesia).

In a few moments, I am going to administer the Oxford, short induction procedure. It is a very fast induction, so as to match the length of time of the CPT.

When you are relaxed, comfortable and hypnotised, I will ask you to place your hand in the cold pressor, remembering the two rules (when to indicate pain threshold and pain tolerance onset). **Do you remember the two rules?** Good. Although, the two rules may not apply, as the feeling of ice cold water may be much reduced during hypnosis, and you may wish to leave your hand in for the full 180secs".

So, if you are ready, I think we will begin.

Do you see the white tape on the curtain (researcher points to a spot on the wall)? That point I will call the target. I would now like you to relax in the chair, keep your head looking straight forward and slowly follow your eyes, just your eyes and not your head, up until they are fixated on the white tape, the target (***remember to keep your head and shoulders facing straight ahead)***, and listen to my voice. Meanwhile, I'll give you some instructions that will help you to relax and focus your attention even more, and gradually enter a state of hypnosis. In order to be hypnotised you need only to stare at the target, follow my voice, focusing your attention, your belief and your creative imagination on my suggestions.

You can become hypnotized if you are willing to do what I ask you to. You have already shown your willingness by coming here today. You can be hypnotized, if you want to be. Just do your best to concentrate on the target, and my words, and let happen whatever you feel is going to take place. Just let yourself go, to what I ask you to think about; if your mind wanders bring your thoughts back to the target and my words. **(1m).**

Staring at the target for this length may start to make your eyes feel a little tired; your eyes may even start to strain a little and you may even find that your eyelids start to

feel a little heavy. You may notice that your eyes are becoming a little watery or even a little dry from the strain. Soon you will have stood the discomfort long enough; your eyelids will feel too tired to remain open. You are becoming more and more relaxed. In a moment, I am going to ask you to take a deep breath in, HOLD it briefly and then take a deep breath out, and I will do it with you. Ready now, breathing in, hold and breathing out. Now, the strain in your eyes is getting greater. It would be a relief just to let your eyes close and to relax completely. You will soon have strained enough and you will welcome your eyes closing of themselves.

Your eyes are now closed. You are going to relax much more... Just keep your eyes closed until I ask you to open them or to wake up.

I am going to count you down from 1 to 10 and at each count you will go deeper in to my suggestion, deeper in to hypnosis, and when I count to 10, you will feel relaxed, comfortable and hypnotised.

1, 2, feeling calm 3, 4, listening to my voice 5, Breathing in and breathing out, 6, more and more relaxed 7, 8, feeling more comfortable, 9, deeper in to hypnosis, 10, now fully relaxed and hypnotised.

You will still be able to open your eyes, speak and move as I give you FURTHER hypnotic suggestions. **(2mins)**

I want you to now open your eyes and rest your hands on your lap. And now look at your hands and wrists. That's right, hands relaxed. Soon, you will submerge your hand and wrist in to the water, and when you do, **you will find that your hand is insensitive to pain. It will be insensitive to pain and no pain sensation will originate from it.** You will be able to keep your hand submersed for the full 180secs, when I will tell you to remove it. That's right, during hypnosis your hand will be insensitive to pain and the feeling of cold and you be will able to keep your hand submerged until the end of the 180 second period, when I will tell you to remove it.

I will count you down from 3 to 1 and on 1, fully place your hand and wrist in to the water, palm facing down and touching the bowl at the bottom. And I will continue to give you hypnotic instruction.

3,2,1 **(18o secs). Hand in the water.**

Suggestions, whilst the hand is in the water: Remember to breathe in and breathe out. Relax the hand and body. Your hand is insensitive to pain. It will be insensitive to pain and no pain sensation will originate from it. You will be able to keep your hand submersed for the full 180secs, when I will tell you to remove it. That's right, during hypnosis **your hand will be insensitive to pain and the feeling of cold a**nd you be will able to keep your hand submerged until the end of the 180 second period, when I will tell you to remove it.

Breathing calmly in and out. Notice how your hands and wrist feel relaxed, how your body feels relaxed. Notice inside your mind. Nice and relaxed. The longer you keep your hand in the water, the more relaxed and good you feel. You are enjoying the sensation of the water on your hand and wrist.

Your hand is insensitive to pain. It will be insensitive to pain and no pain sensation will originate from it. You will be able to keep your hand submersed for the full 180secs, when I will tell you to remove it. That's right, during hypnosis your hand will be insensitive to pain and the feeling of cold and you be will able to keep your hand submerged until the end of the 180 second period, when I will tell you to remove it.

(removal of hand)

Take a nice deep breath and let your eyes close for a moment. Good. I am going to count backwards from 5 to 1 and this experience will end. 5, 4 feeling good 3, 2 ready to open your eyes, 1 Open your eyes slowly and gently, feeling good, feeling completely wide awake. Good, great.

6.5 Appendix E: Participant Debrief Sheet

DEBRIEF - Using Hypnotic suggestion to improve performance on a hand-immersion task

(1) How long did the study take to complete?

Today's study lasted up to 1hr 45mins.

(2) What type of equipment was used?

The CPT used was a blue, Coleman 30 QT performance cooler tank 45x34x39cm, containing ice-water prepared at 2 Celsius (C) (plus or minus 0.05C), with netting that kept ice to the side of the bucket (to prevent direct contact of ice to the hand). The temperature did not fluctuate by more than 0.5 degrees C, as small changes can result in pain response variations. Additionally, a circulating pump, Fluval SEA CP1 circulation pump 1000LPH was used to maintain desired temperature and prevent a microclimate of warm water to build around the hand. A hot water bottle, wrapped in a small blanket was used to warm the hand in. An infrared thermometer was used to take hand temperature. An Omron M2 Basic Intelli Sense, Automatic upper arm blood pressure monitor and cuff, were used as a health and safety check. A household thermometer was used to maintain water temperature. A stop-watch was used to record time pain onset/threshold times (on researcher's mobile phone). *(*WASI) fluid intelligence tests (version 2) block design units and matrices book.

(3) What type of data will be produced?

Pain-threshold and pain-tolerance data will be produced, and both are continuous, numerical data. The three predictors will be frontal executive function scores (Stroop, Hayling and the WASI block design and matrices).

(4) What type of design was used and why?

The study used a within-subjects design, counterbalanced, as each participant needed to repeat the CPT 3 times (to compare the effect of hypnotic analgesia, against a medical analgesia condition and a control condition). The time participants register the onset of pain (threshold) and the time they withdraw their hands (threshold) will be the two dependent variables.

(5) What was the main research question?

This research has tested whether hypnotic analgesia is reliant on frontal lobe function, through the use of frontal lobe tasks, and whether hypnotic suggestion can be used to reduce the feeling of discomfort on a task that

required you to immerse your hands, alternately, in very cold water (The Cold Pressor Task (CPT)) compared to a medical analgesia, proven to reduce the sensation of discomfort and pain. It is expected that performance on the Stroop Task (a left frontal, dominant task) will predict the magnitude of hypnotic analgesia. This prediction will be revealed through pain onset and pain threshold scores, as measured through the use of the Cold Pressor Task. The research question is looking at whether measures of frontal lobe function are predictors of susceptibility to suggestion. While there is current literature supporting a role for frontal executive functions in hypnosis, the data are mixed, and no clear conclusion can be drawn (Parris, 2016). Consequently, more research is needed to understand the mechanisms underpinning this form of suggestion.

The research question is: Is your susceptibility to hypnotic analgesia determined by levels of frontal lobe function? These finding may also have a positive consequence within future clinical and medical settings, regarding pain relief.

(6) Write a brief procedure for the study?

Please use the information in the 'Participant Information Sheet' provided.

PLEASE DO NOT TELL OTHER PARTICIPANTS OF WHAT WAS INVOLVED IN THE HYPNOTIC SUGGESTION, AS IT WILL INVALIDATE THE STUDY.

THANK YOU FOR YOUR PARTICIPATION!

If you wish to find out more about the study, feel free to contact the researchers (contact details below). Also, if you wish to find out the results from the study, the researchers can also be contacted for that purpose.

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