Exploring the Aetiology and Effects of Pharmacological Cognitive Enhancement use in UK University Students

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Contents

Glossary of Abbreviated Terms

Abbreviated Torrance Test for Adults (ATTA)

Attention deficit hyperactivity disorder (ADHD)

Autonomic Nervous System (ANS)

Bacopa monnieri (Bacopa)

Cambridge Neuropsychological Test Automated Battery (CANTAB)

Central nervous system (CNS)

Cognitive enhancement (CE)

Computerised tomography (CT)

Continuous Performance Task (CPT)

Continuous Wave (CW)

Correlational based signal improvement (CBSI)

Deoxygenated Haemoglobin (Deoxy-Hb)

Dextroamphetamine (d-amphetamine)

Dorsolateral Prefrontal Cortex (DLPFC)

Functional magnetic resonance imaging (fMRI)

Ginkgo biloba (Ginkgo)

Hayling Sentence Completion Test (HSCT)

Heart Rate Variability (HRV)

High Frequency (HF)

Hospital Anxiety and Depression Scale (HADS)

Inter-beat Interval (IBI)

Methylphenidate (MPH)

Mild cognitive impairment (MCI)

Millimetres of mercury (mmHg)

Modified Beer-Lambert Law (MBLL)

Nanometer (nm)

Near-infrared Light (NIR)

Oxygenated Haemoglobin (Oxy-Hb)

Parasympathetic nervous system (PNS)

Participant Information Sheet (PIS)

Performance Assessment Battery (PAB)

Pharmacological cognitive enhancement (PCE)

Prefrontal Cortex (PFC)

Rapid Visual Information Processing Task (RVIP)

Region of Interest (ROI)

Remote Associates Task (RAT)

Respiratory sinus arrhythmia (RSA)

Sinus Node (SA node)

Sympathetic nervous system (SNS)

The Multitasking Framework (MTF)

Wisconsin Card Sort Test (WCST)

Abstract

Media claims suggest that use of pharmacological cognitive enhancers (PCE) in UK universities is significant and is increasing, though academic research has come to less consistent conclusions. While there has been expansion of research in this area, the public health impact of long-term PCE use, including the potential for adverse effects to cognitive, neurological and physiological functioning remains unclear. Consequently, this thesis aimed to investigate the aetiology and long-term effects of PCE use in some UK universities. Study 1 aimed to investigate CE use in four UK universities, including: which substances are commonly used, the reasons for use and which factors relate to consumption. Here, caffeinated products were the most popular, followed by modafinil. Furthermore, several sociodemographic and personality variables were part of a statistical model to predict CE use, although only gender, age and moral perceptions of modafinil use were found to be significant. Study 2 focussed on modafinil as the most popular PCE aiming to assess the long-term impact (> 3 months) of use on executive functioning by administering various cognitive performance measures. Despite no behavioural differences on the *2*-back (working memory) and the continuous performance task (sustained attention), modafinil users responded to both horizontal and vertical cues more quickly than nonusers on the cued go/no-go task (inhibitory control) without experiencing an accuracy trade-off or performance decrement. To investigate the neural substrates of any potential cognitive deficits, Study 3 assessed cognitive and neurophysiological processes by using functional near-infrared spectroscopy, electrocardiogram and a digital sphygmomanometer alongside cognitive performance measures designed to increase cognitive workload. It was found that there were no behavioural performance differences on easy and difficult variants of the multitasking framework (stressor) or *3*-back (working memory) between groups, but users experienced significantly lower systolic blood pressure across the tasks and greater haemodynamic change during the *3*-back. Blood pressure indicated that users appeared

less physiologically aroused during performance measures, but increased haemodynamic response compared with controls revealed possible underlying cognitive deficits. Taken as a whole, modafinil appears to be the most popular PCE in the UK for university students, and long-term use unexpectedly revealed enhanced inhibitory control but possible deficits to working memory performance. This research consolidates previous claims about modafinil as the most popular PCE among UK university students. Furthermore, this is the first study to investigate long-term modafinil use and establish behavioural and neurophysiological differences with nonusers.

Chapter 1: An Overview of Substances used for Cognitive Enhancement.

1.1 Chapter Overview

Cognitive enhancement (CE) strategies (also termed neuroenhancement strategies) are techniques used with the intention of enhancing cognitive performance or mood. Numerous CE techniques exist, including use of food supplements, pharmaceutical products and illegal drugs. This chapter explores the different substances which are most regularly purported to enhance cognition and investigates their pharmacology, mechanism of action and estimated level of use. Moreover, for the remainder of the thesis, the term 'cognitive enhancement' refers to the user's intention to enhance performance more so than the efficacy of the substance itself, which will be further explored in Chapter 2 when the pharmacological cognitive enhancement (PCE) modafinil is examined (Maier, Haug, & Schaub, 2016; Maier & Schaub, 2015).

1.2 What are Cognitive Enhancement Drugs?

The most popular CE drugs can be divided into two groups: soft enhancers and PCE. Soft enhancers are popular, legally available substances which include food products, herbals substances and tonics and products containing caffeine. On the other hand, PCE use is often prohibited, and includes synthetic pharmaceutical substances and some illegal drugs (Maier, Ferring & Winstock, 2018). Both CE groups differ in the magnitude of their effect on cognitive performance and in mechanism of action, although variations also exist within each group. Differences between the various CE substances are discussed below, including the primary differences which are apparent between soft enhancers and PCE.

1.2.1 Soft Enhancement

Some soft enhancers are commonplace in society, particularly those products containing caffeine, which is the most widely consumed psychoactive substance in the world (Zhang, Jiang, Liu, & He, 2017). Further to this point, caffeinated beverages are among the most popular caffeine-based products because they act as a minor stimulant and promote feelings of alertness and wakefulness which often become integrated into a person's daily routine. Consequently, it has been suggested that use of caffeine for CE is less explicit than other soft enhancers or PCE (Rosen & Weil, 2004). For example, nutraceuticals (herbal pills and tonics) are more explicitly marketed as CE drugs but are considerably less popular, owing to the fact that these drugs each have medicinal properties that are purported to act differently on cognitive performance and mood with some more successful than others (Rai, Bhatia, Sen, & Palit, 2003; Tsai, Lin, Simon Pickard, Tsai, & Mahady, 2012). Moreover, these substances are less widely obtainable and are often only available at speciality retailers, which suggests that users who seek them do so with a specific intention in mind, one of which could be CE purposes. Of course, nutraceutical drugs are not just marketed as CE substances, they are also lauded for their various physical health benefits (Ward et al., 2019), meaning the reasons for their consumption are not always clear.

Caffeine, a psychostimulant, acts on the autonomic nervous system and shifts dominance from the sympathetic (SNS) to the parasympathetic nervous system (PNS). Unlike PCE, its effects are non-selective as it acts through blocking adenosine receptors (A_1 and A_2) in the prefrontal cortex which in turn promotes monoamine release. As such, the neurotransmitters dopamine, serotonin and noradrenaline are released, which facilitate feelings of wakefulness and alertness (Fredholm, Yang, & Wang, 2017). Therefore, caffeine shares more similarities with pharmaceuticals used for PCE than nutraceuticals which

operate through enzyme synthesis (Ahmed et al., 2016), although effects are less pronounced and the substance has a shorter half-life than PCE (Franke et al., 2017). Notable soft enhancers which contain caffeine include; coffee, energy drinks, caffeine pills and guarana (Maier, Liakoni, Schildmann, Schaub, & Liechti, 2015).

Of the nutraceutical substances, ginseng is perhaps the most popular and has been used in Eastern medicine for thousands of years (Geng et al., 2010). This drug comes from the root of the ginseng plant and can be brewed in tonics and formulated as a tablet, and is popular in alternative medicine because of a variety of medicinal properties, including: lowering fatigue, acting as a powerful antioxidant and boosting the immune system (Scholey et al., 2010). There are two variants of the substance; Panax (Asian) and American ginseng which share many properties but have subtle variations (Scholey et al., 2010). Research has revealed that effects on cognitive performance appear to be linked to constituent saponins called ginsenosides, which are divided into two main groups: protopanaxadiol and protopanaxatriol which vary in concentration between Panax and American ginseng. However, studies suggest that the enhancing effects of the two types are similar, as each has been shown to improve working memory, memory retention and neural plasticity to some degree (Vogler, Pittler, & Ernst, 1999). Furthermore, long-term use may also be neuroprotective as ginseng proliferates antioxidants which are known to prevent cognitive impairment by eliminating free-radical compounds (Ramesh et al., 2012).

Similar to ginseng, ginkgo biloba (ginkgo) is a nutraceutical plant extract which has garnered popularity for its medicinal properties (Major, 1967). This substance can be taken as a dietary supplement and can also be brewed in tonics and made into a tablet. Unlike ginseng, there is little knowledge about the precise mechanism of action of ginkgo, but some evidence suggests that it acts on adrenergic receptors which in turn promote wakefulness and vigilance (Blecharz-Klin, Piechal, Joniec, Pyrzanowska, & Widy-Tyszkiewicz,

2009; van Beek & Montoro, 2009). Moreover, bilobalide is the active saponin identified in the substance which is linked to acute increases in cognitive functioning. Similar to ginsenosides, bilobalide is an antioxidant and free-radical scavenger which increases adenosine triphosphate production which appears to reduce memory impairments and other reductions in cognitive functioning found as a result of mild cognitive impairment (MCI) (Duverger, DeFeudis, & Drieu, 1995). As such, ginkgo has been marketed as a useful drug to combat and slow the memory loss symptoms associated with dementia and Alzheimer's disease which has been supported in a recent systematic review (Yuan, Wang, Shi, & Lin, 2017), although the authors state that benefits are only apparent when the drug is consumed daily for 22 weeks or longer. Furthermore, there is some evidence to suggest that ginkgo does not possess CE properties at all, despite marketing which promotes the drug for this purpose (Canter & Ernst, 2007). Overall, evidence for ginkgo as a CE is not definitive, despite the substance's popularity.

Bacopa monnieri (bacopa) is less popular than ginseng or ginkgo but is purported to have several CE effects. The cognitive effects of the drug resemble ginseng, with improvements observed in various executive functions such as attention and working memory (Stough et al., 2008). Some improvements are also apparent in attentional speed, but these findings are not consistently reported (Kongkeaw, Dilokthornsakul, Thanarangsarit, Limpeanchob, & Norman Scholfield, 2014). Bacosides, the constituent saponins thought to govern the CE effects of bacopa, are similar to ginsenosides as they act as antioxidants and may be neuroprotective with continued use (Calabrese et al., 2008). However, there is limited understanding of bacopa as a CE substance compared to ginseng and ginkgo, as such the effectiveness of the drug cannot be properly determined without further research.

1.2.2 Pharmacological Cognitive Enhancement

Distinct from soft enhancers, PCE are typically synthetic pharmaceutical substances and illegal drugs, whose use is controlled or prohibited by law. Most studies on PCE effects focus on amphetamines, particularly dextroamphetamine (d-amphetamine) which is sold under the popular trade name 'Adderall', and racetams like piracetam. However, evidence in support of these drugs as effective PCE is limited, with the studies that exist identifying only modest enhancements with single periods of use. Effects are often also outweighed by high expectations, suggesting that the efficacy of these drugs does not often exceed user perceptions (Bagot and Kaminer, 2014; Battelday and Brem, 2015; Linssen, Sambeth, and Riedel, 2014). Some research has also looked at use of illegal drugs in the UK such as psychedelics (Elsey, 2017) and cannabis (Franke, Roser, Lieb, Vollmann, & Schildmann, 2016), but as these techniques appear to be rare they will not be discussed further in this Chapter. Instead, the focus will be on substances which are most commonly self-reported by users for PCE, namely, d-amphetamine, methylphenidate (MPH) and modafinil.

Amphetamine is a central nervous system (CNS) stimulant which is used as a treatment for attention deficit hyperactivity disorder (ADHD). D-amphetamine in particular has been identified to have modulatory effects on neurotransmitter networks, predominantly; dopamine, serotonin and noradrenaline (Darracq, Blanc, Glowinski, & Tassin, 1998). Alterations to monoamine neurotransmission are linked to feelings of increased wakefulness and alertness in humans, which has also made the substance useful for the treatment of narcolepsy syndrome in the past (Parkes & Fenton, 1973). Furthermore, in adolescents with ADHD, studies show improved learning outcomes during schooling, owing to a long half-life which extends the overall effect of the drug throughout the day (Pelham et al., 1999). Moreover, dopaminergic drugs like Adderall are shown to positively impact mood, which evidence suggests can increase creative thought processes (Farah, Haimm, Sankoorikal, Smith, & Chatterjee, 2009). Equally, benefits to cognition in healthy people do not appear to be as extensive as with other PCE, although findings are comparatively

limited (Bagot & Kaminer, 2014; Ilieva, Boland, & Farah, 2013). However, users regularly self-report pleasurable experiences with the drug which may contribute to the perception of enhanced cognition (Vargo & Petróczi, 2016; Vrecko, 2013).

Similar to Adderall, MPH is prescribed for ADHD, and to a lesser extent, narcolepsy. Moreover, the pharmacology of both substances is similar, as MPH also modulates noradrenaline and dopamine in the prefrontal cortex which is linked to a reduction of symptoms associated with ADHD, as well as selective improvements in cognitive functioning (Linssen, Sambeth, Vuurman, & Riedel, 2014). In particular, MPH has been shown to be beneficial to cognition in adolescents and adults with ADHD, who exhibit improved reaction time, attention and executive and non-executive memory (Coghill et al., 2014; Storebø et al., 2015). Emerging evidence has also suggested that MPH can ameliorate working memory deficits found in stimulant users, although more research must be conducted in the area to verify these findings (Moeller et al., 2014). With healthy people, studies using MPH to improve cognitive functioning show fewer compelling results. Although, some research indicates that the drug is beneficial to certain cognitive functions, including processing speed, inhibitory control, working memory and memory consolidation (Linssen et al., 2014; Spencer, Devilbiss & Berridge, 2015). While ADHD adolescents gain the most benefits from MPH, self-administration by healthy adults has risen, possibly in an attempt to medicate undiagnosed symptoms of ADHD or to achieve CE, although reasons behind use need to be more comprehensively explored (White, Becker-Blease, & Grace-Bishop, 2006). Nevertheless, this kind of use appears to be relatively safe, as the potential for harm with MPH is seen to be low when taken in clinically safe doses, with the most extreme and commonly reported side effects being appetite suppression and disturbed sleep, which are symptoms frequently associated with stimulant use (Becker, Froehlich, & Epstein, 2016; Jeffers & Benotsch, 2016).

Less popular than MPH or Adderall, modafinil is a novel psychostimulant which is primarily used to treat narcolepsy but is also used for shift work sleep disorder. The mechanism of action of the drug was unknown until recently, where it was found to be a dopamine and noradrenaline reuptake inhibitor, as well as having modulatory effects on histamine in the prefrontal cortex (d-Angelo, Savulinch, & Sahakian, 2007). Despite similarities with MPH and Adderall, modafinil has the longest half-life of the PCE's, lasting approximately 10 – 15 hours, which is considerably longer than Adderall at 3.5 hours (Robertson & Hellriegel, 2003). Modafinil is a prescription drug in the UK and is listed as a controlled substance in the US, restricting its possession by healthy people. However, because it is shown to increase feelings of alertness and wakefulness, research has revealed that is has gained popularity as a CE drug. Moreover, healthy people also exhibit benefits to attentional processes, learning and memory (Sahakian et al., 2015; Turner et al., 2003) and self-report feelings of increased energy and alertness (Stoops, Lile, Fillmore, Glaser, & Rush, 2005). Similar to MPH, it appears to have low potential to cause harm when taken in clinical quantities, however; evidence of doses in excess of clinical guidelines is limited, and thus potential adverse events cannot properly be evaluated (Battleday & Brem, 2015; Rush, Kelly, Hays, Baker & Wooten, 2002).

1.3 Prevalence estimates

Recently, there have been media reports estimating the prevalence of CE substance use. In the UK, an article by a Cambridge University student newspaper reported that of 1,000 University of Cambridge students surveyed, 10% reported use of modafinil, MPH or Adderall for CE. Moreover, one third of the sample were allegedly considering PCE use if the opportunity presented itself (Lennard, 2009). A later article by the popular student website The Student Room (2016) suggested a similar trend on a national scale, with 1 in

10 students self-reporting use of study drugs at least once in their lifetime on an open survey. This anecdotal evidence is corroborated by scientific studies indicating that use of CE substances is increasing in both the US (Advokat & Scheithauer, 2013; Emanuel et al., 2013) and Europe (Maier, Liechti, Herzig & Schaub, 2013). However, robust and comparable estimates of use are difficult to obtain due to the nature in which data is collected. Primarily, survey questions which investigate use lack standardisation, and drugs are not uniformly assessed between studies. Interpreting use is also a challenge, as many prevalence figures do not reveal the reasons behind use (e.g. CE or recreation), which can be further conflated by cultural differences in what constitutes CE drugs. There is also a lack of racial diversity in sample characteristics making generalisability of results challenging, and the limited follow-up studies make it difficult to perform trend analyses.

Limitations notwithstanding, it is clear that use of soft enhancers, particularly coffee and other caffeinated products, is considerably greater than PCE (Maier et al., 2013; Singh, Bard & Jackson, 2014; Wolff, Brand, Baumgarten, Losel, & Ziegler, 2017). Furthermore, lifetime use of PCE among university students in the USA varies from 5 – 55% (McCabe, West, Teter, & Boyd, 2014; Smith & Farah, 2011), but other factors besides CE strategies underlie these estimates. In Europe, prevalence studies have a similarly wide spread of results ranging from 5 – 46%, but interpretation remains challenging, especially given the small number of studies (Schelle et al., 2015). A study in Switzerland found that 14% of respondents reported nonmedical use of PCE substances across their lifetime, however; use in the previous year and month was considerably reduced (Maier et al., 2013). Also considering that most respondents reported that PCE use did not match expectations, it is a reasonable assumption that recent use was limited because CE strategies were not thought to be efficacious. German students exhibit comparatively lower lifetime PCE prevalence rates, which range from < 1 – 20% (Dietz et al., 2013), and in the UK, research has suggested that use is similar, at 5% or below (Holloway & Bennett, 2012; Singh, Bard, & Jackson, 2014a).

However, a recent study and the biggest exploration of international CE use to date, found that between 2015 and 2017, self-reported use of PCEs increased from 1.7% to 5.1%. Further still, use of modafinil in the UK was highest among the 15 countries surveyed, and saw a substantial increase of 3.2% in 2015 to 10% in 2017 which is consistent with previous claims in the media (Maier, Ferris & Winstock, 2018). Prevalence estimates are, however, still limited in the UK, and if media reports are to be believed, more peer reviewed research is necessary to establish an accurate picture of use.

1.4 Chapter Summary

In summary, cognitive enhancement drugs belong to two groups: soft enhancers and PCE. Substances in each group have been discussed separately, in terms of their mechanism of action and pharmacology, with the efficacy of each substance also being briefly touched upon. Experimental studies with nutraceuticals and PCE have, however, shown modest results, but PCE do appear to exhibit acute benefits to some aspects of executive functioning such as working memory and attention. Furthermore, based on prevalence estimates in the UK, modafinil appears to be the most popular PCE, with recent data even showing a considerable increase in use. As such, the efficacy of modafinil will be discussed further in Chapter 2 by examining clinical studies, dose dependent effects and the potential harms of this drug, to further understand the implications on the user. Nonetheless, despite reports by the media which suggest an increase in the use of CE strategies, little robust peer reviewed data exists which supports these claims. Problems with methodology and sample diversity also raises the issue of generalisability, and intentions behind off-label use are rarely investigated making it difficult to interpret prevalence data. As such, a gap in knowledge exists concerning intentions and levels of use of CE drugs in the UK, which was addressed with a cross-sectional national survey which forms the first study of this thesis.

Chapter 2: A Review of Modafinil use in Healthy and Clinical Populations

2.1 Chapter Overview

In the previous chapter, a comprehensive examination of substances used for CE was conducted. Through a combined exploration of anecdotal studies by the media and peer-reviewed scientific research, it was established that pharmaceutical substances, termed PCEs, were appearing to grow in prevalence worldwide. This chapter takes a closer look at the drug modafinil, a PCE which appears to be most prevalent in the UK, and examines research which assesses acute use in healthy and clinical populations in terms of the effects the drug has on cognition and health.

2.2 An Overview of Modafinil

First marketed in France in the 1990's, modafinil was identified as a wakefulness agent promoted for tackling excessive drowsiness (somnolence) in narcolepsy syndrome (Minzenberg & Carter, 2008). A recognised neurological disorder, narcolepsy is characterised by uncontrollable periods of sleep which can be highly disruptive to a person's life, and despite being a rare condition, it affects upward of 30,000 people in the UK (NHS, 2019). Modafinil counteracts the symptoms of this disorder through a unique method of action which targets various neurotransmitter networks resulting in a prolonged wakeful state. By inhibiting the reuptake of dopamine and noradrenaline, modafinil counteracts deficits in orexin found in those diagnosed with the disorder, and prevents inappropriate periods of excessive sleep from occurring (d'Angelo et al., 2017). In light of the drug's success, modafinil has garnered international attention and has been approved in the USA as a schedule IV drug and is also sanctioned to treat sleep apnoea and shift work

sleep disorder which leads to over 1,000,000 prescriptions a year (Minzenberg & Carter, 2008). It is also prescribed for use in the US military, and is given to combat pilots and used by medical doctors completing long shifts (Francis, Wishart, Williamson, & Iverach, 2019; Ooi, Wong, & See, 2019). In the UK, modafinil can only be obtained through prescription and is only sanctioned for narcolepsy treatment, but recent research indicates that off-prescription use is rising (Maier, Ferris & Winstock, 2018). As already explored, reasons surrounding unregulated use are numerous, but the potential health and cognitive consequences of use are not well understood. Consequently, the different populations who use modafinil off-prescription will be further discussed below, including any potential acute benefits or side effects to cognitive performance conferred from use.

2.3 Modafinil effects in Healthy Non-Sleep Deprived Adults

Studies assessing acute use of modafinil in healthy, non-sleep deprived people show mixed results. In some cognitive domains, acute modafinil use benefits cognition. For instance, studies examining working memory performance reveal improved capacity when compared with controls. Müller, Steffenhagen, Regenthal and Bublak (2004) found that on a delayed digit span task, 100 and 200mg doses improved working memory performance and delayed recall compared with a control group who did not receive modafinil. Furthermore, there was no difference in error rate between the groups, suggesting that modafinil improved working memory without a speed/accuracy trade-off. Similar findings have been reported on the backward digit span task, as both Randall et al. (2005) and Turner et al. (2003) found that 100mg and 200mg of modafinil improved working memory performance when compared with placebo. Furthermore, when examining IQ, Randall and Shneerson (2005) found that 100mg and 200mg of modafinil reduced errors on the digit span task in those with lower IQ scores, bringing performance in line with higher performers. These findings

support Müller et al. (2004), who found that on a digit span task and a numeric manipulation working memory task, modafinil (200mg) reduced errors in lower performers without a speed/accuracy trade-off. A later study by the same authors used the same dose of modafinil or a placebo and participants completed an IQ test and spatial working memory task (Müller et al., 2013). Working memory improvements were most pronounced in those with lower IQ, and during the higher difficulty levels of the tasks, implying that modafinil confers most benefits to under-performers and has modest benefits to working memory in already average or high performers. Nevertheless, some studies reveal limited to no benefits on working memory performance. For instance, 2 studies with the backward digit span failed to show an effect with 100mg (Pringle, Browning, Parsons, Cowen, & Harmer, 2013) and 300mg (Winder-Rhodes et al., 2010) doses. Moreover, on tests of verbal working memory, 300mg was shown to not only have no effect on performance, but participants self-reported overconfidence in cognitive ability (Baranski, Pigeau, Dinich, & Jacobs, 2004). The same was found in a 2-week follow-up study which combined 200mg daily administration of modafinil with cognitive training. Despite improvements to new language learning with English neologisms paired with visual stimuli, verbal working memory was not improved, suggesting that modafinil may only improve selective aspects of working memory in rested people (Gilleen et al., 2014).

Studies examining attention and inhibitory control show less consistent findings. On an anti-saccade stop signal task, Rycroft et al. (2007) found that modafinil (200mg) improved response inhibition compared with placebo by reducing response latency. However, response errors were not reduced, suggesting that modafinil did not improve accuracy. Turner et al. (2003) also found reduced latency on a stop signal task and identified a dose-dependent effect with 200mg conferring faster response times than 100mg. Conversely, Theunissen, de la Asuncion Elvira, van den Bergh, and Ramaekers (2009) compared modafinil (200mg) with MPH (20mg) and placebo on a stop signal task, and found that both

drugs in fact slowed response time, thus appearing to reduce inhibitory control, although the effect was non-significant. On tests of simple selective attention, healthy people appear to show limited gain from modafinil. Müller et al. (2004) reported that on a letter cancellation and trail making task, modafinil (200mg) did not improve attention above placebo. Furthermore, on the Cambridge Neuropsychological Test Automated Battery (CANTAB), R andall, Shneerson, Plaha, and File (2003) reported that 100mg and 200mg of modafinil did not improve selective attention compared with placebo, and even increased self-reported anxiety during the task. Additionally, a follow-up study by Randall, Shneerson and File (2005) confirmed these findings, but on a rapid visual information processing task (RVIP), both doses significantly increased sustained attention compared with placebo. Such improvements have also been reported by Turner et al. (2003), who found that modafinil (100mg and 200mg) improved performance on the RVIP and a set shifting task relative to placebo. Furthermore, on a visual and auditory attention shifting task, Marchant et al. (2009) found that modafinil (200mg) improved sustained attention, alertness and attentional speed compared with a placebo condition. Modafinil therefore appears to have some benefits for healthy people in inhibitory control, sustained attention and attentional speed, but not selective attention.

Research assessing creativity and cognitive flexibility appears to show equivocal results. A construct which underlies creativity is problem solving capability, and modafinil does not appear to positively impact this function. Mohamed (2016) administered the Group Embedded Figures Task and the Remote Associates Task (RAT), and Modafinil (200mg) was found not to improve problem solving ability above a matched placebo. Moreover, participants in the experimental condition exhibited a marginal reduction on the Abbreviated Torrance Test for Adults (ATTA) relative to the placebo condition, signifying that modafinil reduced creativity. However, if participants were found to have low creativity at baseline, modafinil increased scores in-line with higher performers.

Nevertheless, on the Hayling Sentence completion test (HSCT), Mohamed and Lewis (2014) found that modafinil (200mg) increased response latency without increasing response accuracy relative to a placebo, indicating that creative thought was slowed. Moreover, Müller et al. (2013) showed that on the ATTA and a line drawing task, a modafinil (200mg) administration group exhibited decreased creativity scores compared with the placebo group, although differences were non-significant. Cognitive flexibility appears to decrease with modafinil, as Randall, Fleck, Shneerson, and File (2004) demonstrated that 200mg significantly increased errors on a set shifting task relative to placebo. As such, in healthy people, modafinil might, in fact, reduce creative thought and cognitive flexibility, which suggests that in order to produce benefits in certain cognitive domains, a trade-off exists in other aspects of performance.

In summary, healthy people show benefits to various cognitive domains with acute modafinil use. Research appears to support increases to working memory performance often without a trade-off to speed or accuracy with moderate doses (200mg) of the drug. Some improvements are also reported in inhibitory control and sustained attention, although research is not as consistent as with studies examining working memory. Moreover, despite these improvements, studies assessing creativity and cognitive flexibility do not only seem to show null results, but moderate doses of the drug appear to decrease these functions. This suggests the existence of a cognitive trade-off, as certain cognitive domains are increased at the cost of others. Furthermore, most benefits seem to be recorded with 200mg doses, with 100mg and 300mg sometimes showing no benefits. This implies that there is an inverted 'U' shape effect with the drug, and that there is an optimum dose (200mg) where healthy people gain the most benefits.

2.4 Modafinil effects in Healthy Sleep Deprived Adults

Modafinil's effects on cognitive performance in sleep-deprived populations are promising, as it has been shown to reduce sleepiness. As with rested people, the drug benefits working memory processes, although there is less available research. For example, an early study by Pigeau et al. (1995) compared modafinil (300mg) with d-amphetamine (20mg) and placebo on 3 different occasions during 64 hours of sleeplessness in military personnel. Modafinil and d-ampetamine improved performance on a digit span task relative to placebo, although working memory was still impaired when compared with performance when rested. A follow-up study by the authors compared the same doses of modafinil and d-amphetamine to a group that was allowed intermittent naps (Friedl, 2000). Drug administration improved performance on a digit span task, in line with non-sleep deprived scores, although the duration of improvement was superior in the drug groups compared to performance following a nap. This indicates that modafinil may restore cognition more effectively than short periods of rest. Furthermore, on the *n*-back task, Thomas and Kwong (2006) found that modafinil (200mg) improved working memory performance after a single night of sleep deprivation. Performance was improved on the 1, 2 and 3-back compared with placebo, but improvements were most pronounced in the 2-back condition. Of course, it is unsurprising that both groups performed well on the 1-back due to the relative ease of the task, but differences on the 2-back suggest the existence of an inverted 'U' shape effect of the drug with sleep deprived people on working memory performance, in that most benefits appear on the moderate difficulty task. Similarly, Sauvet et al. (2019) found that modafinil (200mg), administered 3 times over 18 hours, improved performance on the 2-back relative to a placebo after 40 hours sleep deprivation. Moreover, a compound of modafinil (100mg) and flecainide (9mg), TN102, which modulates the effects of modafinil by reducing cardiovascular activity, was shown to improve wakefulness and working memory performance more than modafinil alone.

Modafinil appears to be most beneficial to attentional processes, reaction time and memory recall in sleep deprivation studies. A body of research by the Institut de Medicine Aerspatiale in France found various benefits to sustaining performance on a large task battery. In the first study, male air force pilots received either 6 treatments of modafinil (200mg) or placebo over 60 hours of wakefulness (Lagarde & Batejat, 1995; Lagarde, Batejat, Van Beers, Sarafian, & Pradella, 1995). On the second study, the effectiveness of modafinil (200mg) and sleep versus a matched placebo and sleep was investigated on the same test battery (Batejat & Lagarde, 1999). Both studies found that modafinil significantly improved attention, reaction time, mathematical reasoning, grammatical reasoning and spatial processing when compared with placebo. Moreover, in the first study, statistical differences were most pronounced after 48 hours of sleep deprivation, which indicates that modafinil is most effective after a significant period of wakefulness. Wesensten et al. (2002) compared modafinil (100mg, 200mg and 400mg) with caffeine (600mg) during 54 hours of wakefulness. Five groups were administered the computerised Performance Assessment Battery (PAB), twice hourly, with 200 and 400mg of modafinil increasing response time and mathematical ability significantly more than placebo and equal to caffeine. Findings suggest that 100mg may not be sufficient to restore cognitive performance in unrested people, but medium and high doses produce similar performance outcomes to a high dose of caffeine. Modafinil (300mg) has also been shown to improve reaction time, memory recall and reasoning in military recruits compared with placebo after 64 hours of shift work (Buguet, Montmayeur, Pigeau, & Naitoh, 1995). Moreover, with doctors in the emergency department, modafinil (200mg) improved sustained attention on the CPT and improved accuracy without a speed trade-off after an overnight shift (Gill, Haerich, Westcott, Godenick, & Tucker, 2006). Moreover, Hart et al. (2006) found that during 3 days of simulated night shifts that 200 and 400mg of modafinil significantly improved divided attention and immediate recall compared with a placebo

when participants completed a battery of tests in day and night cycles. There were no dose-dependent differences in performance, signifying that attention and memory both benefit from moderate and high doses of modafinil when sleep deprived. Interestingly, both doses exerted strongest effects during night-time consumption, which may indicate that this is the optimal time to take the drug.

On measures of inhibitory control and cognitive flexibility, different doses of modafinil shows strong results, although research is limited. Wesensten, Killgore, and Balkin (2005) found that after 85 hours of sleeplessness, a single dose of modafinil (400mg) significantly improved performance and flexibility on the Wisconsin Card Sort Test (WCST) and inhibitory control on the Stroop comparable with caffeine (600mg) and above d-amphetamine (20mg). Furthermore, a study with a medium dose of modafinil (200mg) found reduced errors on the WCST and greater cognitive flexibility and control on the sentence completion test, compared with a matched placebo (Walsh, Randazzo, Stone, & Schweitzer, 2004).

In sum, acute use of modafinil shows promising results across various cognitive domains in otherwise healthy but sleep deprived people. Unrested people appear to be receptive to different doses of modafinil, with moderate (200mg) and high doses (300 – 400mg) exhibiting strong restorative effects across various cognitive functions. Similar to healthy people, working memory performance is also improved, although some evidence indicates that this effect is only apparent in tasks of moderate difficulty and performance is still below when rested. Attentional processes, inhibitory control, reaction time, memory recall, spatial processes numerical and grammatical reasoning are also restored with medium and high doses of the drug, but 100mg doses do not appear to be effective. Moreover, unlike rested people who appear to experience decrements in cognitive flexibility, a moderate dose of modafinil is shown to improve this function is unrested people. Finally, different

doses of the drug even appear to be effective in excessive sleeplessness (54 and 64 hours respectively), suggesting that modafinil is most effective when counteracting sleep deprivation.

2.5 Modafinil effects in Adults with Clinical Conditions

The effects of modafinil on cognition in clinical populations has also been studied. For instance, research appears to show the reversal of working memory deficits commonly reported in patients with chronic schizophrenia. In a double-blind, placebo matched study, modafinil (200mg) administered alongside antipsychotic medication significantly improved performance on the digit span and backward digit span tasks (Turner, Clark, Pomarol-Clotet, et al., 2004). Delayed visual recognition memory was also improved on the CANAB and the modafinil group showed improved attentional set shifting on the Tower of London task. People with Schizophrenia have also exhibited improvements on the *n*-back with modafinil (100mg) relative to placebo, which fMRI revealed was linked to increased activation of the dorsal anterior cingulate cortex (Spence, Green, Wilkinson, & Hunter, 2005). Moreover, working memory improvements have also been reported on a letter-number sequencing task, when schizophrenic patients received a continuous, 28 day dose (days 1- 14 100mg, days 15 – 28 200mg) (Rosenthal & Bryant, 2004). Additionally, modafinil led to mood enhancement and a significant reduction in fatigue during baseline measurements, but no differences were reported between 100 or 200mg treatments. Furthermore, Minzenberg et al. (2009) found that modafinil (200mg) improved inhibitory control relative to placebo on a stop signal task, which was linked to greater activation of the PFC. Modafinil has also been found to reduce some negative symptoms of schizophrenia as outlined by the DSM-IV, although findings are mixed. A longitudinal study from 2002 to 2006 found that in people with schizophrenia and schizoaffective disorder, 8

weeks of once-daily modafinil (200mg) significantly reduced symptoms of sleep irregularity, and improved sustained attention on a degraded performance-continuous performance test and verbal recall on the Californian Verbal Learning Test, all deficits commonly reported in the disorder (Pierre, Peloian, Wirshing, Wirshing, & Marder, 2007). Furthermore, modafinil did not improve psychosis reported on the Scale for the Assessment of Negative Symptoms (SANS) or the Brief Psychiatric Rating Scale (BPRS), but nor did it negatively impact symptoms, suggesting that the drug has effective but limited treatment utility for schizophrenia, and is not reported to degrade the condition. However, a systematic review by Saavedra-Velez, Yusim, Anbarasan, and Lindenmayer (2009) found that other studies reported no reduction in negative symptoms at all with different doses of the drug. Although, in these studies improvements to various aspects of cognition were reported, including sustained attention, attention shifting and short-term memory. However, not all studies show benefits to cognitive processes in patients with schizophrenia. An fMRI study with schizophrenic patients with prominent negative symptoms revealed that modafinil (100mg) did not improve Cognitive control on a motor activity task (Hunter, Ganesan, Wilkinson, & Spence, 2006). Furthermore, an 8 week follow-up study showed no improvements to attention or working memory with once-daily modafinil (200mg) compared with placebo (Sevy et al., 2005). Nevertheless, studies indicate that modafinil at different doses can improve cognitive performance, and some associated symptoms, of schizophrenia.

In people with depressive disorders, a small number of studies reveal that modafinil has some effectiveness, particularly for mood enhancement. For example, modafinil (400mg) taken once daily for 3 days, improved subjective ratings on the Positive and Negative Affect Schedule and a generalised mood scale in depressed but otherwise healthy people relative to placebo (Taneja, Haman, Shelton, & Robertson, 2007). Although, negative affect was also seen to significantly increase, as participants reported greater feelings of anxiety.

However, with patients from an out-patient clinic experiencing major depression, Price and Taylor (2005) demonstrated that subjective feelings of anxiety and depression were reduced with one daily treatment of modafinil (50 – 450mg doses) after 2 weeks and 3 months of treatment as reported on the Beck Depression Inventory, Zung Self-Rating Scale and Hamilton Depression and Anxiety Rating Scale. Similarly, in patients with bipolar depression, Ballenger (2009) found that daily modafinil (average dose 177mg) significantly improved symptoms of depression relative to a placebo on subjective responses to the Inventory of Depressive Symptoms. Although, modafinil did not reduce incidences of mania or hypermania. In addition, on cognitive performance, evidence for improvements with modafinil is very limited. On the Stroop, modafinil (100 - 400mg) has been shown to improve inhibitory control and reduce interference compared with placebo (DeBattista, Lembke, Solvason, Ghebremichael, & Poirier, 2004). Finally, on the CANAB, which examines working memory, episodic memory, sustained attention and planning, modafinil (200mg) significantly improved performance on working memory and episodic memory, relative to placebo in people with remitted depression, but not on other measures (Kaser et al., 2017). Modafinil, therefore, appears to have positive outcomes in alleviating low mood and feelings of depression and anxiety in people with clinical conditions, but more research is required which inspects cognitive performance.

In people with ADHD, the drug has been shown to significantly decrease attention deficits associated with the disorder. In children with the condition, Rugino and Copley (2001) found that daily modafinil (200mg) for an average of 4.6 weeks significantly decreased ADHD score on the ADHD Rating Scale-IV. Furthermore, Rugino and Samsock (2003) showed that children receiving a lesser dose of the drug (100mg), after 6 weeks of daily treatment, exhibited a significant decrease in symptoms as rated on the Conners Rating Scale. Moreover, in children who were assessed daily at school and home, modafinil (170 – 425mg) was found to decrease symptoms of the disorder on the ADHD Rating Scale-IV in

both environments, although decreased appetite, weight loss, insomnia and headaches were reported as side effects (Greenhill et al., 2006). In another study, modafinil (170 – 425mg) decreased scores on the ADHD Rating Scale-IV and Conners Rating Scale and appeared to be particularly effective at significantly reducing inattentiveness and hyper-active impulse in the children compared with placebo. Finally, research investigating cognitive performance in the lab is rare, but one study with adults with ADHD found that modafinil (200mg) was associated with improvements in spatial planning, visual recognition memory and working memory on a battery of cognitive tasks, compared with a placebo group (Turner, Clark, Dowson, Robbins, & Sahakian, 2004). As such, modafinil appears effective at reducing disruptive symptoms of ADHD in children, but studies assessing cognitive performance are lacking.

To summarise, in adults with clinical conditions modafinil is shown to be effective at improving cognitive functions impacted by various psychiatric disorders. Many of the studies use daily dosing regimens, which make comparisons with healthy and sleep deprived populations difficult, as most research with those samples are acute administration studies. Nevertheless, like the other populations discussed, working memory performance appears to be improved in people with chronic schizophrenia with 200mg repeat doses of modafinil, as does attention shifting and inhibitory control to some extent. Furthermore, alongside antipsychotic medication, modafinil appears to have some effectiveness at reducing the negative symptoms of schizophrenia, although 100mg doses appear to be ineffective. In adults with depression, modafinil is mainly effective as a mood enhancer and is shown to alleviate low mood and anxiety. Finally, with ADHD children and adults, low and high doses of the drug appear to reduce attention deficits and other associated symptoms of the disorder, and in adults 200mg has also been seen to improve working memory, visual recognition memory and spatial planning.

2.6 Side Effects and Potential Harms

In the populations discussed above, modafinil appears to be well tolerated and facilitates some aspects of cognitive performance while reducing several symptoms of various clinical conditions. Nevertheless, in periods of acute use, certain side effects are reported. In small to moderate doses (100 – 200mg), studies do not describe adverse reactions; however, with larger doses (300mg and above) some common side effects have been observed. The most frequently reported side effects are headaches, nausea and sleep disturbances, which have been found in rested (Saletu et al., 1989; Saletu, Grünberger, Linzmayer, & Stöhr, 1986) and sleep deprived people (Caldwell, Caldwell, Smyth, & Hall, 2000). Anxiety, nervousness and racing heart rate are less observed, but have been recorded in 2 studies (Caldwell, Smith, & Brown, 2004; Wesensten et al., 2005). In a single case, hallucinations have been reported with a large dose of 900mg, although they were also later reported with placebo (Chapotot, Pigeau, Canini, Bourdon, & Buguet, 2003), suggesting that an expectancy effect may have been responsible. Consequently, no severe side effects have been reported in research, and at the time of writing, there have been no reports of serious adverse reactions or death from use of the drug. Nevertheless, Provigil, the official licence holder of modafinil in the USA, has published several guidelines surrounding safe use (FDA, 2007). Moreover, the US Food and Drug Administration point out that research on the long-term health impact of the drug (above 3 months) has not been conducted, but short-term clinical trials show no negative impact on cardiovascular or cognitive health. Of course, the absence of evidence does not equate to the absence of harm, and caution should be taken when repeatedly using any psychoactive substance over a significant period. It is also worth considering that modafinil is a psychostimulant which shares similarities with amphetamine and other neurotoxic substances, and despite not having an identical method of action, drugs known to modulate dopamine and noradrenaline are

proven to lead to physiological and psychological distress, and can result in addiction (Gawin & Ellinwood, 1988). If then, the prevalence reports discussed in the previous chapter about the rise in nonmedical modafinil use in the UK are true, then users potentially find themselves at an elevated risk. Further research is therefore required to assess the impact of long-term use (longer than 3 months), and to evaluate whether modafinil is harmful.

2.7 Chapter Summary

As a cognition enhancing substance, modafinil appears to have some benefits for improving cognitive functions in healthy people with or without sleep deprivation, and in people with various clinical conditions. Evidence is perhaps most persuasive in people who are unrested, as modafinil appears to reverse cognitive deficits associated with sleeplessness to baseline levels or just below. However, in healthy people, evidence for the drug's effectiveness at improving cognitive function is not conclusive. Research supports working memory improvements in a laboratory setting, but effects of modafinil on inhibitory control and attentional processes are less consistent. In addition, creativity and cognitive flexibility show impairments with modafinil use, suggesting that there may be a cognitive 'trade-off' when healthy people use the drug. In terms of dose-dependent effects, 200mg appears to be the optimal dose for conferring cognitive benefits, with doses below and above this amount showing some null results, suggesting an inverted 'U' shape effect. Adverse side effects also appear to be rare but are reported with larger doses of the drug (300mg and above), suggesting that a moderate dose is also the safest. Finally, the long-term impact of modafinil on health and cognition has not been addressed in previous research, despite short-term use (3 months and below) indicating that the drug is well tolerated. Nevertheless, if the prevalence estimates explored in the previous chapter are to

be believed, then there is a recent and substantial increase in modafinil use. Such a rise could come with hidden implications for health and long-term cognitive functioning, particularly if users do not follow medical guidelines for safe use. Therefore, studies 2 and 3 of this thesis further investigate people who report long-term use of modafinil, and they assess cognition, physiological and neurological functioning during completion of various cognitive performance measures. Furthermore, the following Chapter will examine the use of various methods for measuring cognitive workload, an umbrella term for examining different aspects of cognitive performance in response to task difficulty (e.g., working memory, multi-tasking and problem-solving), to determine which methods are most appropriate for capturing potential differences that might be apparent between long-term modafinil users and nonusers.

Chapter 3: Subjective, Cognitive and Neurophysiological indicators of Cognitive Workload: Examining the different methodologies.

3.1 Chapter Overview

This chapter explores the psychophysiological and neurophysiological correlates of cognitive workload, including a variety of neuroimaging and physiological techniques designed to measure cognitive effort. Additionally, highly demanding cognitive performance measures which increase effort investment are discussed here, including research in different types of substance users, to examine whether or not these measures are effective at detecting differences in performance in these groups. This Chapter therefore scrutinises the most effective methods for use in Study 2 and 3 of the thesis for examining potential differences in cognitive workload with long-term modafinil users.

3.2 Defining Cognitive Workload

Cognitive workload can be understood as the level of cognitive effort invested in a task in an attempt to successfully complete it (Cain, 2007). The level of workload required is therefore set by the individual and is not preset by the task. To further clarify, a task does not inherently possess a prerequisite level of workload in order for it to be completed; this is determined by the individual and may vary as a function of who is attempting the task (Vidulich & Tsang, 2012). As such, there is a point in which a person reaches peak effort investment, which represents their maximum cognitive workload. Anything above this level of effort exceeds a person's ability to attend to and process the requirements of the task, and this point has been termed *cognitive overload* (Kirsh, 2000). Furthermore, the point in which cognitive overload occurs has been shown to vary with different populations, such as

substance users, a point which will later be returned to (Cain, 2007). In the following sections of this Chapter, the various methods of measuring cognitive workload are evaluated.

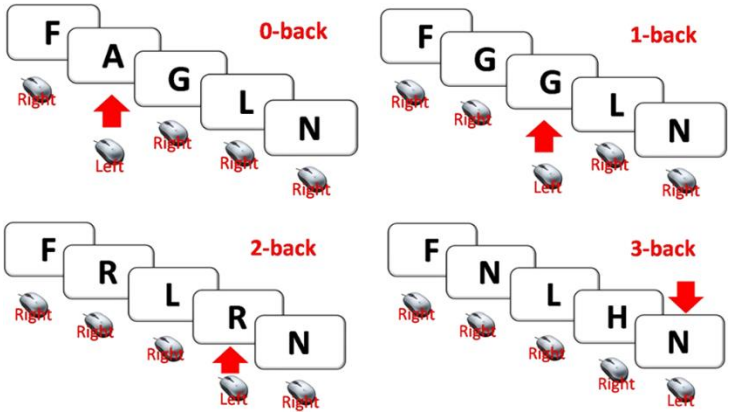
3.3 Subjective and Behavioural Measures of Cognitive Workload

A popular subjective measure of cognitive workload is the NASA Task Load Index (NASA-TLX), which assesses perceived workload across 6 domains (Hart & Staveland, 1988). This measure was developed by NASA to determine workload during complex aviation trials, but has seen growing use in healthcare settings and cognitive research (Tubbs-Cooley, Mara, Carle, & Gurses, 2018). Visual analogue scales investigate self-reported mental, physical and temporal demand, as well as maximum effort, perceived performance and frustration (See Chapter 7 for full description). A review of 550 studies over 20 years found that almost all studies assessed measures of cognitive performance, with 31% focusing on workload with computer-based cognitive performance measures (Hart et al., 2006). Moreover, 6% of studies also assessed other measures of cognitive workload against the NASA-TLX, including neurophysiological measures like cardiovascular reactivity, brain activity and skin conductance. As such, the NASA-TLX is treated as the benchmark with which other cognitive workload measures are compared (Hitt, Kring, Daskarolis, Morris, & Mouloua, 1999). However, like other self-report measures, common criticisms of the NASA-TLX include issues with report bias, honesty and introspective ability. Consequently, cognitive workload is best measured alongside other methods, such as cognitive tasks and neurophysiological measures of effort investment.

Working memory tasks are another effective measure of cognitive workload (Engle, Kane, & Tuholski, 1999). Characterised as the ability to maintain attention and remember specific stimuli in the presence of distracting information, working memory performance is strongly

associated with cognitive workload (Baddeley, 1992). Furthermore, *n*-back tasks are especially effective at capturing effort investment and working memory load because conditions can be altered to systematically increase workload, which can reveal the point in which a person experiences cognitive overload (Jaeggi, Buschkuehl, Perrig, & Meier, 2010). The *n*-back requires constant updating of working memory to recall the position of a stimulus (e.g. a spatial location or letter/number in a sequence) and whether the information currently displayed is a match or non-match (see Figure 3.1.). A recent meta-analysis found that the *n*-back is often used in conjunction with neuroimaging techniques to capture neurophysiological correlates of cognitive workload (Redick & Lindsey, 2013). Nonetheless, this test appears to be an effective working memory task at increasing working memory load, and has been used to demonstrate differences in cognitive workload with clinical populations and chronic substance users (Martin et al., 2018; Sanvicente-Vieira, Kommers-Molina, De Nardi, Francke, & Grassi-Oliveira, 2016). The previous chapter also highlighted that the *n*-back and other tests of working memory have demonstrated performance differences with acute modafinil use relative to placebo. As such, the task may also be sufficient to identify differences in working memory load with long-term modafinil users.

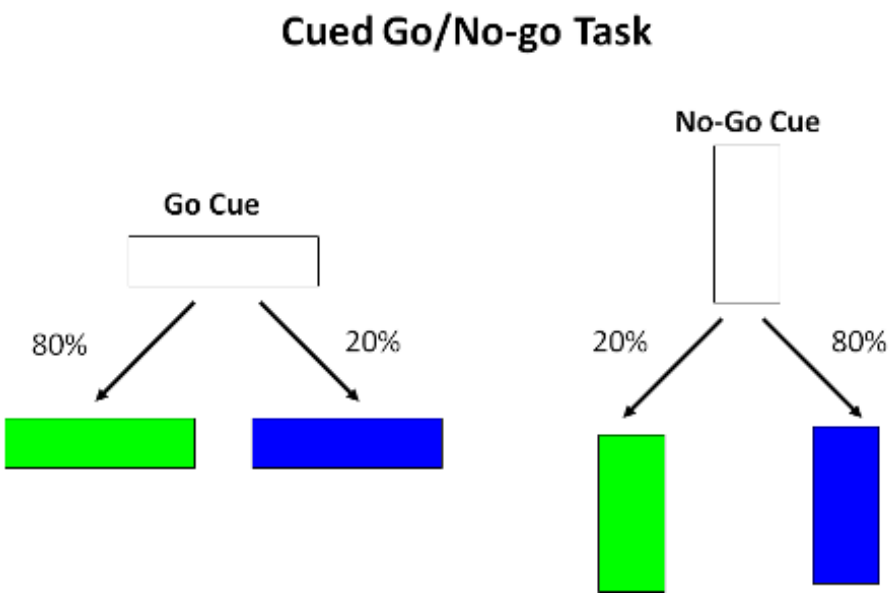
Figure 3.1. – Different conditions of a computerised letter-based *n*-back working memory task. Participants are required to click each time the current stimulus matches the letter '*n*' back in the sequence. As the target becomes more distant, memory interference and the presence of distracting information makes the task demand greater which leads to greater cognitive workload.



Inhibitory control tasks can also be manipulated to increase cognitive workload (Chmielewski, Mückschel, Stock, & Beste, 2015). These tasks require a response to certain stimuli, while simultaneously inhibiting/withholding responses to others. A popular inhibition task is the Go/No-go task, which presents 'go' signals, which require a response, and 'no-go' signals which require withholding a response (see Chapter 4 for full methodology). Differences in inhibitory control are observed by variations in response time between 'go' signals and 'no-go' signals, and in errors in inhibition where participants accidentally respond during 'no-go' trials. Increased response latency during sustained inhibition could indicate mental fatigue in response to increased workload (Kato, Endo, & Kizuka, 2009). Impairments in the ability to inhibit responses are common characteristics in psychopathology and substance abuse. A combined meta-analysis and systematic review of Go/No-Go tasks assessed 318 studies investigating 11 different psychiatric disorders, including substance use disorders, and found that when compared with healthy controls, the task exposed significantly more errors and slower response times in psychiatric samples

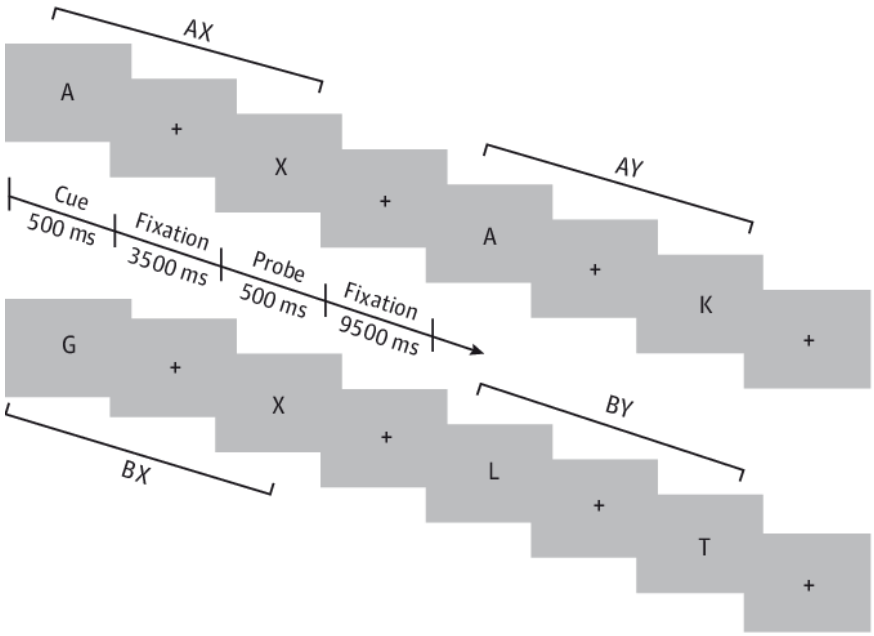
(Wright, Lipszyc, Dupuis, Thaypararajah, & Schachar, 2014). Moreover, research specific to substance users shows that chronic methamphetamine users demonstrate impaired latency to 'no-go' targets (Monterosso, Aron, Cordova, Xu, & London, 2005), as do heavy social drinkers when compared with light drinkers (Ahmadi et al., 2013), and cocaine users during harder task difficulties (Kaufman, Ross, Stein, & Garavan, 2003). As such, substance users, particularly chronic stimulant users, demonstrate deficits to inhibitory control on the Go/No-go task, which could yet be seen in other substance using populations such as modafinil users. A frequent criticism of the Go/No-go task, however, is that it is more a measure of sustained attention than response inhibition (Wright, Lipszyc, Dupuis, Thaypararajah, & Schachar, 2014) and that errors are attributed to plateaus in attention processes rather than deficits in inhibitory control.

Figure 3.2. – A variant of the Cued Go/No-go task. In this version, participants are required to respond only to green rectangles which appear in either horizontal or vertical orientation. Horizontal rectangles appear primarily green, while vertical rectangles are mostly blue. Cognitive workload is created by determining which rectangles to respond to and which to ignore (Fillmore, 2003).



Nonetheless, tests measuring sustained attention have different characteristics to those measuring inhibitory control. These tasks are based on the simple premise of focusing attention over a duration of time to identify specific stimuli, such as letter sequences or number pairs (Shalev, Ben-Simon, Mevorach, Cohen, & Tsal, 2011). Such tests increase cognitive workload by causing the participant to invest sustained effort and vigilance for a long period of time, which leads to mental fatigue and can result in cognitive overload (Szalma, 2009). A popular test of sustained attention is the CPT, which requires participants to attend to strings of letters or numbers and to identify specific patterns (e.g., odd and even numbers), while simultaneously ignoring distracting information (see Chapter 6 for full methodology). This test was designed to measure deficits in sustained attention in patients with traumatic brain injury and psychiatric populations (Rosvold, Mirsky, Sarason, Bransome Jr, & Beck, 1956), with the earliest example presenting letter sequences and requiring patients to respond when 'X' or 'AX' was displayed. CPTs have been used alongside neuroimaging techniques to localise regions of the brain implicated in attentional processes, and to measure psychophysiological indicators of cognitive workload (Adler et al., 2001; Thermenos et al., 2005). The CPT also shows sensitivity to attention deficits found in adults with ADHD (Riccio & Reynolds, 2001), although a recent meta-analysis showed that the task is not sensitive to differences in attentional load between genders (Hasson & Fine, 2012). Research with chronic substance use has also been conducted, and focuses on attention deficits in children who experienced prenatal substance abuse, including alcohol (Dolan, Stone, & Briggs, 2009), heroin and cocaine use (Ackerman et al., 2008; Bandstra, Morrow, Anthony, Accornero, & Fried, 2001), although only prenatal heroin and cocaine use demonstrate impairments to attentional load. Furthermore, the previous chapter showed that acute administration of modafinil improved performance on a CPT in sleep deprived adults, although this task has not been used to demonstrate differences in attentional load with long-term use.

Figure 3.3. – An early variant of a CPT where participants respond only when 'A' and 'X' appear sequentially. Workload demand is heightened by gradually increasing the frequency with which X follows A, resulting in a state of heightened sustained attention (Lesh et al., 2015).



Multitasking paradigms are another effective way of increasing cognitive workload, as these tests require high effort investment and the use of multiple, simultaneous cognitive processes (Manhart, 2004). These tasks are also effective stress inducers, as participants often must attend to multiple highly demanding tasks at once, and errors are often punished by loss of incentives or decreasing scores. However, multitasking cognitive tests lack standardisation, and as such vary in what aspects of cognitive performance they assess and the ease with which they are completed. Nevertheless, the emphasis with these tasks is not on what aspects of cognitive function are being examined, but that the executive is being loaded/overloaded by a series of high demands (Wetherell & Carter, 2014). A substantial body of research exists which demonstrates that multitasking in different forms is an effective means of increasing cognitive workload by challenging a person's ability to

attend to the requirements of several tasks at once (Puma, Matton, Paubel, Raufaste, & El-Yagoubi, 2018; Sanjram, 2013; Wilson & Eggemeier, 1991; Xie & Salvendy, 2000). However, at the time of writing, there is a lack of review data which compares multitasking cognitive performance measures in effectiveness for increasing cognitive workload, although a task has recently emerged which has been shown to increase workload and some associated psychobiological markers. The Multitasking Framework (MTF) (Wetherell & Carter, 2014), is a versatile multitasking model, which enables the simultaneous completion of up to 4 different cognitive performance measures (see Chapter 7 for full methodology). Difficulty can also be altered by changing task parameters (e.g. increasing the length of sums on a mental arithmetic task or increasing speed on a visual monitoring task), and altering the timeframe that participants must complete the tasks. A numerical score is also kept in the centre of the window which updates in real-time and can enter negative values if participants falters across any of the tasks, a method shown to increase cognitive stress and workload by increasing the urgency to perform well (Wetherell & Carter, 2014). As the MTF is relatively new, research with the task is still growing, but some evidence suggests that it is an effective tool for increasing perceived workload and biomarkers of stress (Kelly-Hughes, Wetherell, & Smith, 2014; Wetherell & Carter, 2014; Wetherell, Craw, Smith, & Smith, 2017). Furthermore, in substance using samples, the MTF has been shown to increase perceived workload in ecstasy users compared with controls (Wetherell, Atherton, Grainger, Brosnan, & Scholey, 2012) and increase haemodynamic response, a biomarker of increased cognitive workload, in ecstasy polydrug users relative to a control group (see below for more on the MTF and haemodynamic response with fNIRS) (Roberts, Wetherell, Fisk, & Montgomery, 2015). As such, multitasking methods appear to be an effective means of increasing cognitive workload by increasing effort investment and cognitive stress and reveal differences in cognitive performance between substance using samples, which could be a useful method when examining modafinil users.

3.3 Neurological Indicators of Cognitive Effort

Neuroimaging technologies are useful tools for elucidating neurological correlates of cognitive deficits and increased cognitive workload (Ranchet, Morgan, Akinwuntan, & Devos, 2017; Unni et al., 2015). The technology for which there is most evidence is electroencephalogram (EEG), which demonstrates an increase in theta band and a decrease in alpha band power when cognitive workload is increased (Puma et al., 2018). This method has proven very effective when measuring attention (Borghini, Astolfi, Vecchiato, Mattia, & Babiloni, 2014; Kamzanova, Kustubayeva, & Matthews, 2014; Zhao, Zhao, Liu, & Zheng, 2012) and working memory load (Başar, Başar-Eroglu, Karakaş, & Schürmann, 2001; Kahana, 2001; Klimesch, 1999), and is considered the most widely researched indicator of cognitive workload (Ke et al., 2014). Nevertheless, novel techniques could confer additional benefits when investigating cognitive workload.

Functional near-infrared spectroscopy (fNIRS) is a neuroimaging technique which measures haemodynamic response to neuronal activation via a process termed neurovascular coupling (See Chapter 4 for full methodology). Moreover, studies reveal that fNIRS is sensitive when localising cognitive impairments in working memory and executive function (Ehlis, Bähne, Jacob, Herrmann, & Fallgatter, 2008; Izzetoglu, Bunce, Onaral, Pourrezaei, & Chance, 2004). The area of the cortex thought to govern these functions is the dorsolateral prefrontal cortex (DLPFC), which is deeply innerved with dopamine transporters which are related to cognitive performance (Collins, 2008). Therefore, there is a theoretical basis for use of fNIRS to measure changes in haemodynamic response, specifically oxygenated (oxy-Hb) and deoxygenated haemoglobin (deoxy-Hb), localised to the DLPFC. Moreover, changes in haemodynamic activity can index increases in effort and cognitive workload and can provide a neuronal link of cognitive impairments. Furthermore, tasks which typically

require greater cognitive workload are often sensitive to the presence of cognitive deficits which are linked to substance use (Ranchet et al., 2017). Therefore, by exposing substance users to tasks of differing workload, specific cognitive impairments can be studied, and fNIRS can be used to measure these deficits.

Studies using fNIRS to index cognitive deficits and workload in ecstasy and ecstasy polydrug users have revealed compelling results. Roberts and Montgomery (2015a) examined ecstasy users' executive access on an oral variant of the Chicago World Fluency Test and found increased oxy-Hb change on the left DLPFC and right medial PFC in users relative to nonusers. No behavioural differences were apparent which suggests that users exhibited increased effort investment and activity in the PFC as a compensatory mechanism for ecstasy induced cognitive deficits. Another study by the same authors had similar findings on a random letter generation inhibitory control task (Roberts & Montgomery, 2015b). Ecstasy users showed increased oxy-Hb change on the left and right DLPFC and right medial PFC, despite no behavioural differences. Moreover, recency of ecstasy use significantly predicted increased oxy-Hb change across 2 channels on the right PFC, suggesting that recent substance use is most associated with the presence of cognitive deficits. Montgomery, Fisk, and Roberts (2017) also showed a difference in oxy and deoxy-Hb change on a verbal and spatial working memory updating task. Again, the left and right DLPFC showed increased oxy-Hb change in users, despite no differences on the behavioural measures. Total use and recency of use were also linked to most haemodynamic changes, suggesting again that recent and chronic ecstasy use was most detrimental to cognition. Conversely, Roberts et al. (2015) found that on an intermediate difficulty condition of the MTF, which used mental arithmetic, stroop, visual tracking and visual warning subtasks, ecstasy polydrug users exhibited decreased oxy-Hb change when compared with controls on the left and right DLPFC, and with non-ecstasy polydrug users on the right DLFPC. There were no differences in perceived workload on the NASA-TLX or in performance on the

subtasks of the MTF, suggesting that on an acute multitasking stressor, ecstasy users required less cognitive effort than the other groups to achieve equivalent results. These findings may diverge from other studies as cognitive multitasking is linked to bilateral cortical activation more so than completing single tasks (Deprez et al., 2013), and it may be that users need to invest less effort to access both hemispheres than nonusers, but use more for single cortex activation. This also supports a notion that substance users experience changes in patterns of neural activation which may come as a result of unresolved cognitive deficits. Taken as a whole, studies with ecstasy users show that through changes in haemodynamic response, fNIRS can detect cognitive workload differences in substance users across a range of cognitive performance measures and can even identify deficits linked to chronic and recent drug use. Therefore, despite the current lack of research, fNIRS appears to be an appropriate technology to study potential differences in workload with modafinil users.

Although fNIRS studies have not explored modafinil use, or nonmedical prescription stimulant use in general, a small number have looked at populations with deficits to working memory and executive function, such as adolescents with ADHD. For instance, Moser, Cutini, Weber, and Schroeter (2009) found increased oxy-Hb change in the right DLPFC during a Stroop task with MPH abstinent ADHD adults compared with healthy controls despite a lack of performance differences on the task. Interestingly, Ehlis et al. (2008) observed reduced activation of the ventrolateral prefrontal cortex (VLPFC) in ADHD adults compared with healthy controls on a working memory *n*-back task, with controls also outperforming ADHD adults on the task. They also found the same oxy-Hb reductions and behavioral differences during a verbal fluency task, suggesting that deficits in executive function are coupled with decreased haemodynamic response in the VLPFC. Furthermore, Monden et al. (2012) observed haemodynamic differences in ADHD adolescents pre and post MPH administration on a go/no-go task. MPH led to a general increase in oxy-Hb in

the right PFC which was not apparent before administration. Increased activation in the right PFC was also associated with improved task performance, providing strong support for a link between oxy-Hb change in the region and improvements in executive function. As such, fNIRS shows adequate sensitivity to differences in cognitive workload with ecstasy polydrug users and ADHD adults. Nevertheless, it remains to be seen whether fNIRS can capture differences in neurovascular coupling with nonmedical modafinil users.

3.4 Physiological Indicators of Cognitive Effort

Physiological measures of effort investment are also linked to changes in cognitive workload. These methods vary but tend to focus on the heart's reactivity to cognitive performance measures. Moreover, a recent systematic review of physiological measures used to index cognitive workload reported that no single method stood out as the primary means of measuring working memory, but rather a combination of techniques was most effective (Charles & Nixon, 2019). Popular physiological measurements for capturing changes in cognitive workload are heart rate and heart rate variability (HRV), with some studies also assessing blood pressure (Ranchet et al., 2017). An increase in cardiovascular activity is associated with an increase in cognitive effort, and the use of stress-inducing multitasking tests show the strongest outcomes (Wetherell et al., 2017). For example, Wetherell and Carter (2014) administered 3 difficulty conditions of the MTF (low, medium and high) to 20 healthy people, and found that alongside subjective reports of increasing workload on the NASA-TLX, heart rate, systolic and diastolic blood pressure showed significant increases as the task difficulty increased. Furthermore, Wetherell et al. (2017) demonstrated that the added stress of performance evaluation during the MTF increased cardiovascular reactivity. At specific intervals during the task, participants were informed that they were under-performing compared to average and had to quickly improve their

score. This resulted in significant increases in perceived workload, heart rate and systolic and diastolic blood pressure when compared to the regular MTF condition. Similarly, Kelly-Hughes et al. (2014) found that multitasking under higher difficulty caused significant increases in beat to beat blood pressure than low difficulty multitasking. Moreover, increased working memory load is an effective stressor and cause of cognitive overload, with high heart rate and blood pressure linked to increased working memory demand (Martens et al., 2019; Mehler, Reimer, & Coughlin, 2012). HRV is also affected by cognitive stressors, which has been demonstrated on a flight simulator, with reduced high-frequency HRV as the task increased in difficulty (Durantin, Gagnon, Tremblay, & Dehais, 2014), and on various working memory tasks, including the *n*-back, where harder paradigms also show decreased HRV (Backs & Seljos, 1994; Hansen, Johnsen, & Thayer, 2003; Mulder & Mulder, 1981). Finally, some evidence indicates that tasks of inhibitory control, such as the Stroop, reduce HRV (Egner & Hirsch, 2005; Mathewson et al., 2010), although it has also been shown that this link may be attributed purely to attentional processes (Fairclough & Houston, 2004).

Despite physiological measures of cognitive workload showing some compelling findings, at the time of writing, studies appear to have not looked at differences among substance user samples. Nevertheless, long-term use of illicit drugs are linked with cardiovascular reactivity and toxicity, and may result in episodes of cardiac tachycardia, dysrhythmia, hypertension and even myocardial infarction (Richards et al., 2016). Moreover, stimulants in particular activate the SNS through norepinephrine and adrenergic receptors which increase myocardial oxygen demand and are observed to raise heart rate and systolic blood pressure (Stankowski, Kloner, & Rezkalla, 2015). Studies assessing the effects of stimulant use on HRV in healthy adult users are rare and those that exist primarily focus on chronic prenatal use without assessing differences in workload, as such it is difficult to draw relevant conclusions from this research (Koenig, Menke, Hillecke, Thayer, and Jarczok,

2015). Still, as a prescription stimulant, it is feasible that long-term modafinil use may take a similar toll on cardiac functioning as illegal stimulants, particularly since the drug activates the SNS for prolonged periods (McClellan & Spencer, 1998). Research is therefore required to clarify the effects of modafinil on physiological processes, and to determine whether popular measurements of cardiovascular reactivity, heart rate, HRV and blood pressure are sufficiently sensitive to record drug-specific differences in cognitive workload.

3.5 Chapter Summary

In the previous chapters, CE drug use was comprehensively explored and the effects of acute modafinil use on cognitive functioning was evaluated. This chapter sought to build on the investigation into modafinil use started in the previous chapter by determining the most effective ways to measure cognitive performance in long-term users of the drug. By examining which methods effectively increase cognitive workload and which can detect differences between substance users and controls, it appears that a mixture of subjective, behavioural and neurophysiological measures is most effective. The NASA-TLX is the most established technique for measuring workload but is the most flawed, due to issues inherent to self-report measures, although findings are promising when it is used alongside other methods. With cognitive performance measures, tests of; working memory, inhibitory control, sustained attention and multitasking paradigms are also shown to effectively increase cognitive workload, with promising results seen with the *n*-back, go/no-go task, CPT and MTF, respectively. While EEG appears to be the neuroimaging technique with the most evidence for recording increases in effort and workload, fNIRS is a significantly newer technology which has shown compelling results when examining DLPFC activity in substance using samples. No single physiological method stands out when measuring cognitive workload, but changes in HRV and blood pressure are linked to

increasing cognitive workload, although as of the time of writing, little research exists with substance users despite chronic stimulant use appearing to negatively impact these functions. The following chapter will link the methods evaluated here to the wider aims and methodology of the thesis, and the apparatus used in each empirical study will be discussed in detail.

Chapter 4: Research Aims and Methodology

4.1 Chapter Overview

The previous chapter evaluated the best methods for measuring cognitive performance and cognitive workload in substance using samples. Building on this assessment, this chapter describes the individual neurophysiological methods, along with their theoretical concepts, chosen to investigate cognitive function in long-term modafinil users and the usefulness of survey data for collecting reliable information of substance use behaviour. Furthermore, the aims of the thesis are outlined here, as are the empirical studies designed to address them.

4.2 Research Aims

The principal aim of this thesis is to investigate the use of cognitive enhancement drugs. To accomplish this, several additional aims must first be outlined which address different aspects of CE drug use. From the literature reviewed in this thesis, four overall research questions emerge, which must be addressed in order to explore CE use broadly. These four aims form the foundation for 3 research studies, and are as follows:

(1) To investigate aetiology of CE use among UK university students, in terms of which substances are being used, the reasons for use, as well as other factors potentially associated with consumption. This question is explored in study 1 of the thesis, via a multi-site cross-sectional survey in 4 UK universities (see Chapter 5).

(2) To assess the effects of long-term modafinil use on executive functioning. Study 2 of the thesis addresses this question with use of cognitive performance tests to measure executive function (see Chapter 6).

(3) To explore the effects of long-term modafinil use on neurophysiological processes in the DLPFC, heart rate variability and blood pressure during cognitive testing. In study 3, fNIRS, ECG and a digital sphygmomanometer are used to measure these neurophysiological processes and address this aim (see Chapter 7).

(4) To examine the relationship between changes in cognitive performance and neurophysiological reactivity, and to determine if cognitive performance can be used as a proxy for neurovascular activation. Study 3 addresses this question by using cognitive performance and neurophysiological measures concurrently (see Chapter 7).

To address the aims detailed above, several hypotheses have been formulated. As CE use is a complex and wide-ranging topic, hypotheses have been generated to be study specific. Furthermore, where there is an absence of direct evidence for a hypothesis, specifically in the case of predictions relating to modafinil use, hypotheses have been derived from substances which are chemically similar, such as studies which examine illicit stimulant use. Chapter 1 defined different categories of CE drug and explored their levels of use in the UK and internationally, including factors relating to consumption. In Chapter 2, acute administration studies with modafinil in different populations were discussed. Although research indicated that acute modafinil use was not harmful with medically recommended doses, there was limited evidence on prolonged use. Therefore, predictions about the effects of long-term modafinil use on cognitive functioning were derived from those studies

which focused on better understood stimulants, such as cocaine and amphetamine. Chapter 3 discussed how cognitive performance was related to neurophysiology and cognitive workload. Studies investigating the effects of modafinil on cognitive performance and neurophysiology are limited, but stimulant users' exhibit impairments in neurocognitive function and complications to the cardiovascular system which are not present in healthy controls. As such, similar findings were anticipated with long-term modafinil users on measures of fNIRS, ECG and blood pressure. All hypotheses are outlined in the respective empirical chapters.

4.3 Introduction to Methods

This thesis is primarily concerned with the effects of CE substances on behaviour, cognitive and neurophysiological performance. In the lab, it was investigated how modafinil users compare to non-users with respect to: cognitive performance, cortical haemodynamic response and cardiovascular physiology. To assess different aspects of cognitive performance a wide range of measures were used which are fully detailed in their respective chapters (see Chapter 6 and Chapter 7), each loading on different facets of attention and executive function. The neurophysiological methods were primarily chosen as a proxy for recording cognitive workload (see Chapter 3), and as an index of cognitive effort. For instance, fNIRS is capable of taking readings of haemodynamic changes in the DLPFC, and via neurovascular coupling, capturing changes in mental effort (Tachtsidis & Scholkmann, 2016). ECG provides a measure of heart rate and autonomic reactivity, in addition to heart rate variability as an index of parasympathetic control (Electrophysiology, 1996). Furthermore, taken together, these recordings allow cognitive workload to be measured in a multidimensional way using neurophysiological and psychophysiological means.

4.4 Survey Method

Survey methods can provide a wealth of data on subjective attitudes, intentions and behaviours and can provide in-depth demographic information about respondents. These methods are particularly useful when investigating phenomena that cannot easily be recorded in a lab, such as controversial topics like sexual behaviour and patterns of substance use. However, several limitations exist with self-report measures, which raise questions of validity and reliability, such as social desirability/ demand characteristics when subject matter is stigmatised and poor response rates. Nevertheless, this type of design enables research that would otherwise be difficult to conduct, and is very accessible to researchers (Fan et al., 2006). There are various ethical implications when research investigates sensitive topics or recruits vulnerable samples which makes questionnaire-based studies a useful tool. For instance, in terms of investigating illicit substance use, it is not possible for the researcher to conduct lab-based studies where drug handling and administration are a feature, due to the legal status of many substances. Obtaining a license to acquire and administer a controlled substance such as modafinil is also very difficult, and is not often feasible as part of a time-constrained research project such as a PhD, due to issues that might arise in obtaining ethical clearance from university based or NHS ethics committees. Expense is also an issue, as drug synthesis is costly and not accessible as part of a PhD programme. Vulnerable and prohibited substance using samples are also difficult to recruit because of stigmas and issues of anonymity in the laboratory. It is therefore easier to use questionnaire-based methods that can be distributed online or via mailing lists which enable anonymous responses. Laboratory based research is also limited in terms of its ecological validity, as it does not represent naturalistic behaviour, particularly in terms of environments and situations that users would usually administer

substances. On the other hand, questionnaires provide an alternative for respondents to self-report in-depth information about patterns and frequency of drug use.

There are numerous examples of substance use studies which use survey methods to identify specific user samples, such as the Global Drug Survey which is the biggest survey of its kind in the world (L. d'Angelo, Camilla, Savulich, & Sahakian, 2017; L. J. Maier, J. A. Ferris, & A. R. Winstock, 2018a; Maier, Liakoni, et al., 2015; Maier, Wunderli, et al., 2015). While others combine survey and experimental methods to examine user groups' behavioural and cognitive performance (Montgomery, Fisk, Newcombe, & Murphy, 2005; Carl Roberts & Catharine Montgomery, 2015). The current research uses a similar methodology, first by administering a cross-sectional online survey to investigate general CE use patterns (see Chapter 5), and then by using a battery of questionnaires during a lab-based study to identify user groups and to index drug use behaviour (see Chapter 6 and 7).

4.5 Neurophysiological Apparatus

4.5.1 Functional Near-Infrared Spectroscopy (fNIRS)

fNIRS is a technique designed to measure changes in oxy-Hb and deoxy-Hb associated with neuronal firing, a process referred to as neurovascular coupling (Tachtsidis & Scholkmann, 2016). This is measured by beaming near-infrared light (NIR) through transmitters which are spaced out across the scalp and forehead and make direct contact with skin. Light penetrates up to 6 cm from the surface of the head, and can access 3 mm of cortical tissue density, passing through the scalp, skull and cerebrospinal fluid (CSF), enabling a superficial reading of cerebral activity via a banana-shaped path from transmitter to sensory receiver (Firbank, Okada, & Delpy, 1998). fNIRS is therefore capable of capturing neurovascular activation in the upper regions of the cerebral cortex, such as the DLPFC (Scholkmann &

Wolf, 2012). NIR light must pass through divergent tissue matter before reaching the superficial brain layer, which causes light to scatter. However, due to the unique optical properties of NIR light, changes in oxy-Hb and deoxy-Hb levels can be calculated. Oxy and deoxy-Hb have unique wavelength signatures under NIR light because of their varying concentrations of chromophores. Thus, light absorption is altered based on changes in haemodynamic activity and return signals experience unique attenuation if regions under observation show changes in oxy-Hb and deoxy-Hb, which provides an index of neurovascular activation (See Figure 4.2). The optimum wavelength for measuring haemodynamic change is in the 650 – 950 nanometer (nm) range (Scholkmann et al., 2014). Both oxy-Hb and deoxy-Hb share an absorption co-efficient of 800nm (the isosbestic point), which represents the point at which chromophores attenuate light equally (Zijlstra, Buursma, & van Assendelft, 2000). Therefore, oxy-Hb change is calculated in wavelengths below this co-efficient, and deoxy-Hb in wavelengths above. Preferred wavelengths may differ based on hardware and theoretical differences between researchers, although ranges fall in the NIR window (oxy-Hb 650 – 800; deoxy-Hb 800 – 950 nm). Wavelengths below the optimum range are too easily absorbed by haemoglobin, and the same is true of water when the range is exceeded (Scholkmann et al., 2014). Therefore, reliable measurements are contingent on the appropriate wavelength selection (see Figure 4.1).

Figure 4.1 – Wavelength frequencies of light in nanometers. The optimum NIR spectrum is highlighted in blue (650 – 950 nm) although the standard nominal wavelengths are 765 (oxy-Hb) and 855 nm (deoxy-Hb).

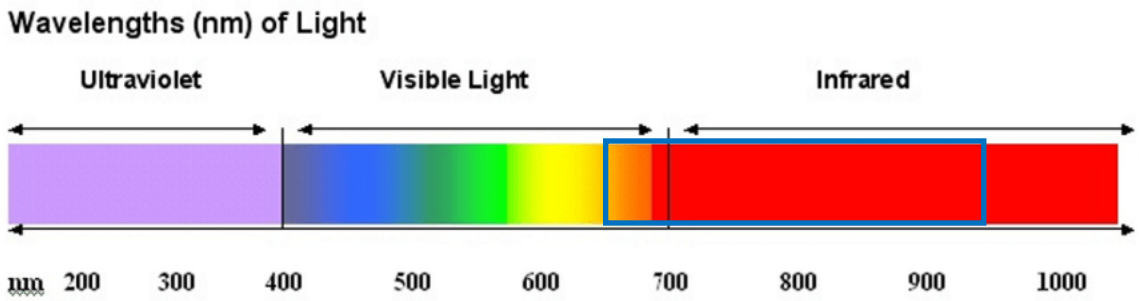
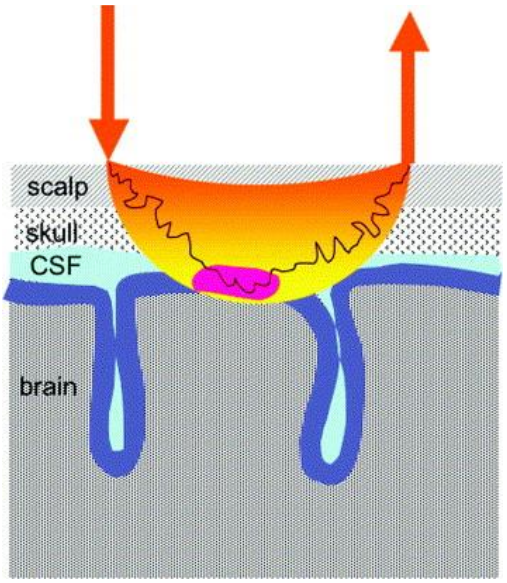


Figure 4.2 – Continuous wave NIR light path length through the head. Light travels via a banana-shaped curve from transmitter to receiver, passing through several tissue layers of the head and returning information about cortical haemoglobin levels in specific areas of interest (denoted as the pink area) across the cortex (Hoshi & Michael, 2005).



4.5.1.1 Modified Beer-Lambert Law

The modified Beer-Lambert Law (MBLL) is a calculation used to measure changes in chromophore concentrations, specifically oxy-Hb and deoxy-Hb (Kocsis, Herman, & Eke, 2006). The MBLL stipulates that changes in light density are constant with changes in chromophore concentrations. However, this calculation has been revised from the original form (The Beer-Lambert Law) to consider light scattering properties in divergent tissues, such as the human head, which is comprised of differing tissue layers of varying density (i.e., scalp, skull and CSF). This method accounts for divergent tissues by calculating the photon mean pathlength through scattering tissues as an estimate for actual photon pathlength (Baker et al., 2014). The statistical formula is as follows:

$$A = \log_{10} \frac{I_0}{I_1} = \alpha \, l \, c \, \mathrm{DPF} + G.$$

In this equation, light attenuation (A) is calculated by dividing light intensity (I_0) by detectable light intensity (I_1). This equals the differential path length factor (αlc DPF) plus what is accounted for in light-scattering loss (G) (Matthews, Pearlmutter, Wards, Soraghan, & Markham, 2008). However, it should be considered that although differing tissue layers are accounted for in the equation, the MBLL is not a perfect model for determining absolute haemodynamic response, as changes are only compared against a baseline measure. As such, fNIRS is considered a relative and not absolute measure (Scholkmann et al., 2014).

4.5.1.2 Current configuration

Due to the importance of the DLPFC in mediating higher cognitive processes, particularly in aspects of executive function and working memory (Carpenter, Just, & Reichle, 2000), and because of the relevance that this forebrain region has to the current research, a 12 channel fNIRS configuration was selected that was placed across the forehead (see Figure

4.3). The configuration used a black fNIRS cap fitted with 3 receivers and 8 transmitters (11 optodes in total) which were fully adjustable by the researcher, allowing for optode placement to be readjusted to fit more comfortably with the shape of each wearer's head while making sufficient contact with the scalp. Transmitters and receivers were spaced at 2.5 cm distance on the cap which was also padded and made from sponge to cushion the sensor placement and reduce pain or skin imprinting as optodes were metal. To reduce ambient light interference, an additional black headband was applied over the optodes which covered the entire forehead (see Figure 4.4). The OxyMon fNIRS system by Artinis Medical Systems was used and data was recorded and analysed using the accompanying Oxysoft software package. This hardware takes topographical readings of up to 6 cm deep (3-4 cm recommended with fNIRS), with a data sampling rate of 500 Hz. The standard nominal wavelengths are outlined in diagram 4.1, though they can be adjusted (default wavelengths were used in this study). Optodes also transmit data using high-speed fibre optic cables, and the software allows for up to 50 Hz frequency readings.

Figure 4.3 – The 12 channel (C) configuration mapped across the PFC, relative to the positioning of transmitters (T) and receivers (R). One channel equals the path between one transmitter and one receiver. Three regions of interest (ROI) are also depicted: the right PFC (orange) medial PFC (green) and left PFC (purple).

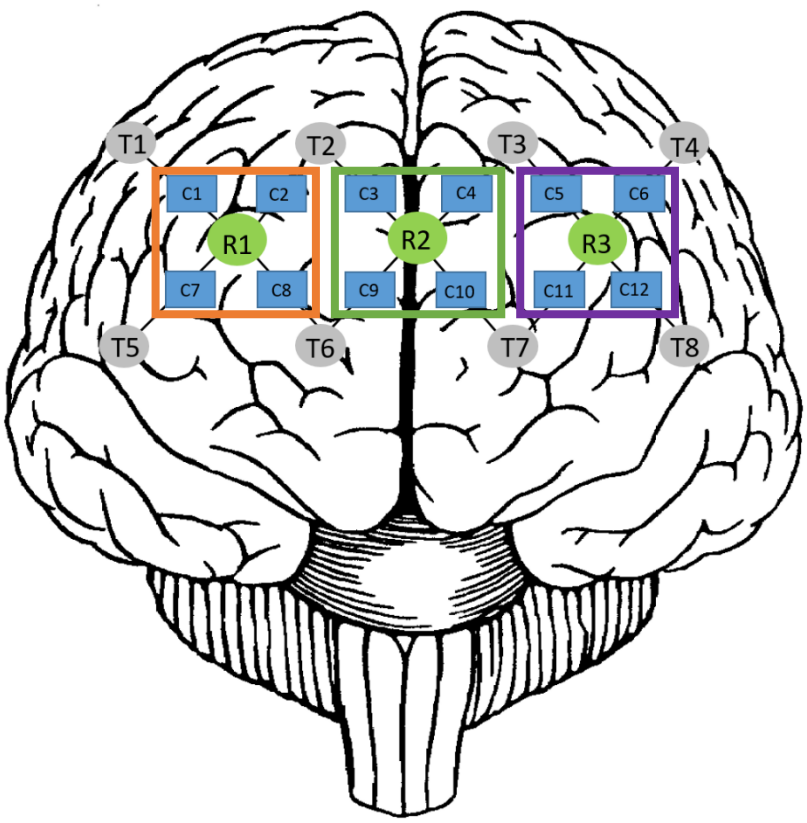
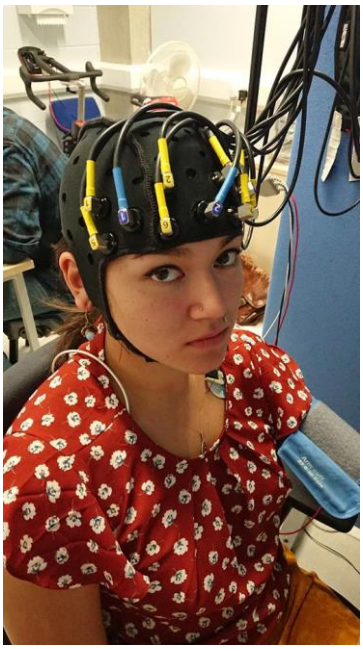


Figure 4.4 – The fNIRS cap as it appears on the wearer's head with transmitters (blue) and receivers (yellow) spaced across the PFC.



4.5.1.3 Signal Processing Technique

Raw data was processed for analysis using the OxySoft accompanying software analysis package. A low-pass filter of 0.1 was applied to eradicate noise stemming from physiological artefacts, such as heartbeat frequency and blood pressure changes, and a high-pass filter of 4 was also used to minimise noise from muscle and eye movement. Data was acquired at a 50 Hz sampling rate, and average oxy-Hb and deoxy-Hb calculations were taken for the baseline period and for each cognitive performance measure. OxySoft produced oxy-HB and deoxy-Hb averages in Microsoft Excel format and then the correlational based signal improvement (CBSI) method was applied to the raw data which reduces signal noise interference by introducing a correction to average haemodynamic change calculations. Without such a correction, signal quality can be contaminated by

motion induced noise, which can cause oxy-Hb and deoxy-Hb signals to become more positively correlated when they should typically be strongly negatively correlated. Thus, fNIRS produces 3 separate components: (a) the true signal measuring haemodynamic response, (b) noise (motion induced and other kinds) which mimics haemodynamic changes, (c) and white noise. The CBSI aims to capture (a) only, and improve the overall quality and reliability of the signal (see Cui, Bray, and Reiss (2010) for a full review of the signal processing method and statistical formula). As such, after running the formula in an Excel document, a single oxy-Hb change value was then produced (deoxy-Hb values were not required as they were inverse values of oxy-Hb counterparts) and data was exported to SPSS Version 25 for statistical analysis.

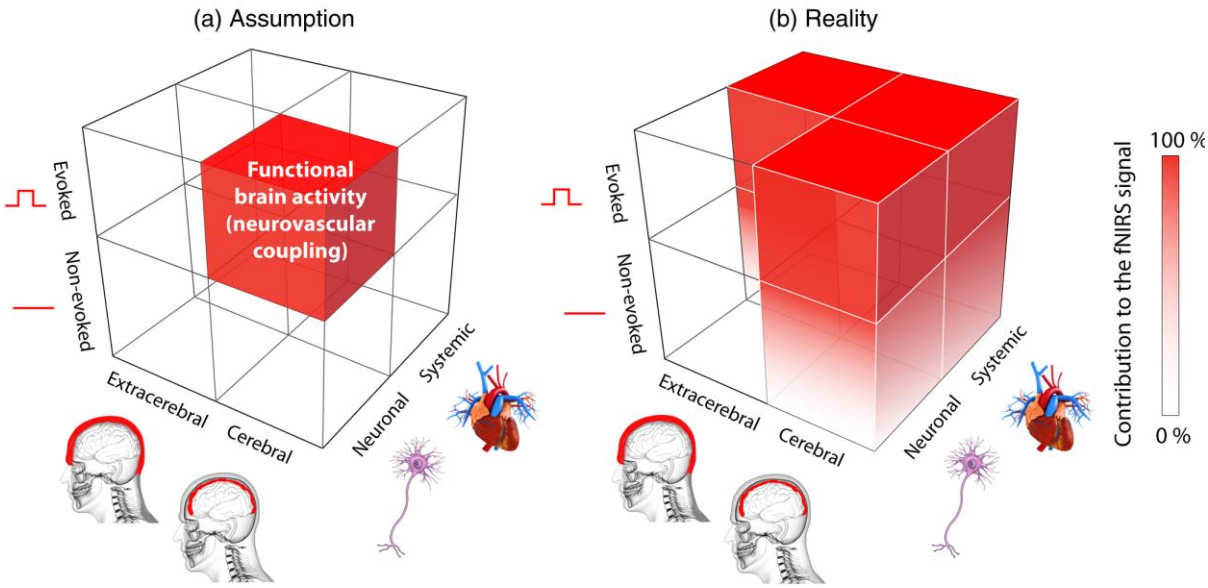
4.5.1.4 Strengths and Limitations

fNIRS is a non-invasive, continuous wave (CW) neuroimaging technology that imposes less physical constraint than established methods like functional magnetic resonance imaging (fMRI) and computerised tomography (CT) scanning as the user is not confined within apparatus. This can allow for data collection under realistic conditions as subjects can complete tasks involving robust body movements, enabling participation in a wider range of tasks than fMRI would allow. The DLPFC is accessible to fNIRS, allowing measurements of higher cognitive function to be made in more true-to-life settings (Leff et al., 2011). Moreover, fNIRS has superior spatial resolution when compared to EEG, allowing for a deeper image of neuronal activity (Anwar et al., 2016). The affordability of the technology also increases its accessibility for research, making fNIRS increasingly popular in neuroimaging studies (Yang & Chen, 2013).

Although fNIRS is a useful neuroimaging technology, various limitations can be ascribed to its use. Chiefly, as previously mentioned, CW devices cannot take absolute measurements of haemodynamic response, even when using the MBLL to account for scattering light in

divergent tissues, as findings are only compared against a baseline period. Furthermore, recordings suffer from a poor depth resolution when compared with fMRI, as optodes can only measure up to 3 mm depth underlying the skull (Anwar et al., 2016). Additionally, temporal resolution is poor with haemodynamic measurements, particularly when compared with EEG (Leff et al., 2011). Signals from fNIRS are also sensitive to the extracerebral layers, such as the hair and scalp. Tests of cognitive function, which are increasingly used with fNIRS, can increase ANS activity, which can produce non-neuronal driven haemodynamic changes in the extracerebral layers and thus contaminate NIR signals which can lead to the occurrence of false positives and negatives (Fairclough, Burns, & Kreplin, 2018; Hoshi & Michael, 2005) (see Figure 4.5). These changes can also occur due to the discomfort of optode attachment against the scalp, which can create participant stress leading to ANS activation (Tachtsidis & Scholkmann, 2016). Hair has also been found to influence fNIRS signals, as certain pigmentations readily absorb NIR light more than others. Head movement must also be accounted for as this can create movement artefacts and dislodge optodes which can lead to ambient light bleeding, a cause of signal interference (Hoshi & Michael, 2005).

Figure 4.5 – The assumption and the reality of the components which comprise an fNIRS signal. Extracerebral and systematic activity are potential confounders in all fNIRS research but are particularly problematic if the ANS is stimulated. As such, fNIRS can be highly susceptible to other physiological influences (Scholkmann et al., 2014).



4.5.2 Electrocardiogram (ECG)

ECG is a technology that records electrical activation of the heart by monitoring potential changes on the surface of the skin. These changes are created by a process of polarisation and depolarisation of the heart, initiated by specialised pacemaker cells which begin this process. Polarisation occurs when electrolytes infuse cells, charging the cell membrane with an electrical current. Depolarisation is therefore the process of cell membrane discharge, when electrolytes leave the cell and spread through the myocardium. ECG detects atrial and ventricular muscle excitation, which causes heart muscle contraction. Throughout the process of polarisation and depolarisation, the tissues surrounding the

heart conduct an electrical current, causing an echo of cardiac activity which is detected at the skin by electrodes and captures an image of the heart in motion (Pflanzer & McMullen, 2016).

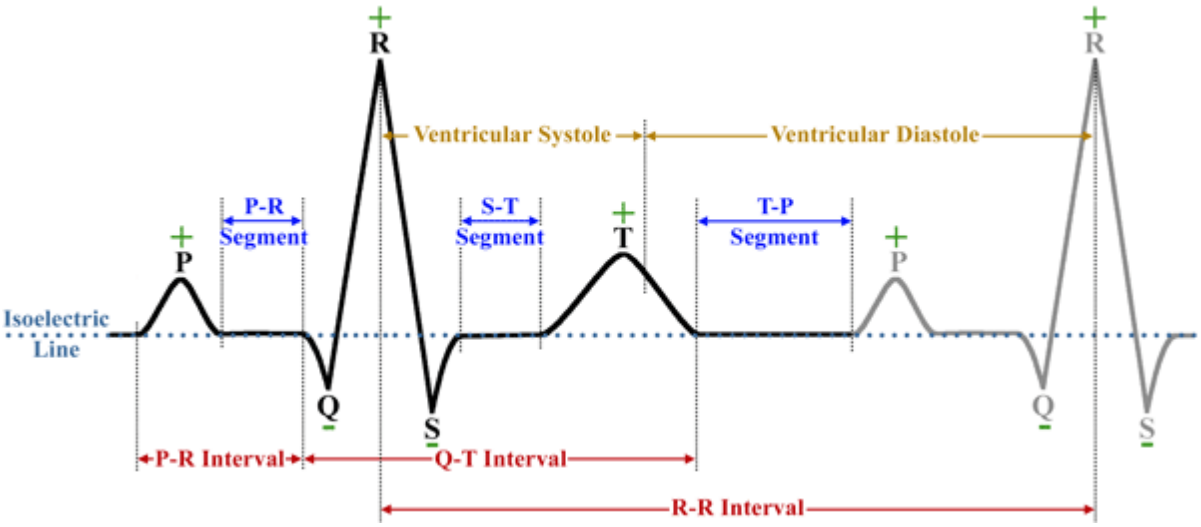
4.5.2.1 The ECG Trace

An ECG trace captures the electrical activity of the heart, specifically the process of polarisation and depolarisation. A single waveform (see Figure 4.6) illustrates the P wave, QRS complex and T wave. The P wave is the first event recorded and signals the depolarisation of the atrial muscle; usually lasting 80-100 milliseconds. The P-R interval, an isoelectric period (the short zero voltage period) immediately following the P wave and before the QRS complex begins, is the time between atrial depolarisation and the time the impulse needs to travel to the ventricle, this lasts between 120-200 milliseconds. The QRS complex begins immediately afterwards and shows ventricular depolarisation, a rapid process between 60-100 milliseconds. The ST segment is the isoelectric period following the QRS, when the ventricular muscle is completely depolarised. The T wave is the final event in a single waveform and represents ventricular repolarisation, which lasts longer than depolarisation but is not normally measured. Instead it is common practice to record the Q-T interval, the period of depolarisation and repolarisation of the ventricle, which lasts between 200-400 milliseconds, but varies based on heart rate (Klabunde, 2011). A single waveform is a cardiac action potential, and a rhythm strip is a measurement of repeating waveforms which is typically how ECG is recorded. Heart rate variability can be measured by recording the time variations between successive R peaks on a rhythm strip, called the R-R interval, or sometimes the inter-beat interval (IBI), which can be used to index changes in heart beat and the autonomic nervous system (ANS).

4.5.2.2 Introduction to Heart Rate Variability

HRV is a measure of variability in the time period between successive heart beats which can be observed with ECG, and was first proposed as a reliable measure of distress and premature mortality in fetal research (Horn & Lee, 1965). The decades following have since increased focus on HRV as an indicator of the heart's reaction to changing circumstances brought about by often unpredictable stimuli (Acharya, Joseph, Kannathal, Min, & Suri, 2007) and as an effective index of attention and mental effort (Berntson et al., 1997). HRV can be measured at 3 distinct frequencies: very low frequency, low frequency and high frequency. Very low and low frequency contributions to HRV include: thermoregulatory processes, vascular auto-rhythmicity, haemodynamic response delays and the renin-angiotensin system (blood pressure control) (Berntson et al., 1997). High frequency measurements are indexed by respiratory sinus arrhythmia (RSA), a respiratory pattern which increases the sinus rate during inspiration and decreases it with expiration. RSA is controlled by parasympathetic activity at the sinus node (SA node) in the heart, which can provide information on cardiac vagal control (also termed vagal tone) (Berntson, Cacioppo, & Grossman, 2007). Respiratory-frequency rhythms create changes in the discharge frequency of the SA node, which intrinsically relates RSA to breathing patterns. Vagal innervation of the SA node therefore leads to respiratory inhibition, reducing PNS control of cardiac functioning, which can be assessed by observing variations in R-R intervals on a continuous ECG trace (Berntson et al., 1997). As such, HRV is a robust psychophysiological method for indexing changes in parasympathetic control.

Figure 4.6 – A typical ECG trace, and the individual components demarcated. A cardiac action potential is recorded in the depolarization and repolarization of the atrial and ventricular muscles. An ECG trace can also be used to measure HRV by observing spatial differences between R peaks (Pflanzer & McMullen, 2016).



4.5.2.3 Current Configuration

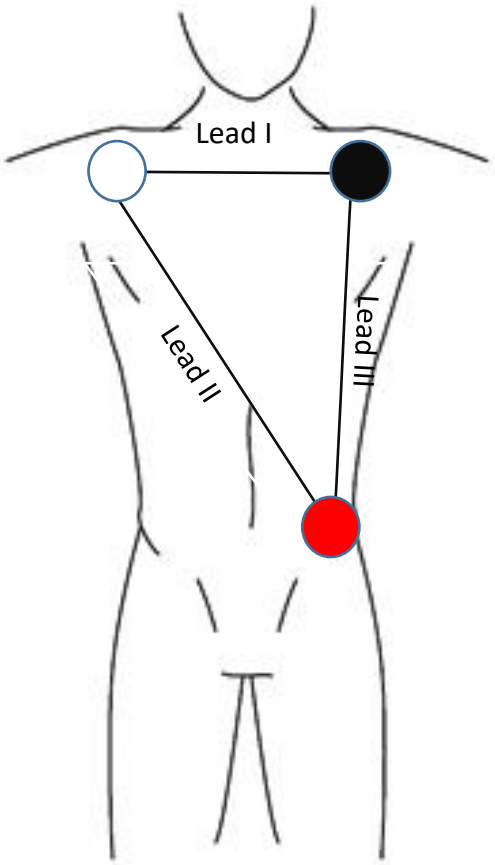
As this research focused on neurovascular indicators of increases in cognitive effort, a 3-lead Biopac ECG was used to capture changes in heartrate variability. Three electrodes were placed across the torso: two below each collar bone and one above the hip. Pinch clips were attached to the electrodes: positive (right collar bone), negative (left collar bone) and earth (above the hip). This configuration conforms to Einthoven's Triangle (see Figure 4.7) which demonstrates appropriate electrode placements to capture echoes of the heart (for further details on the principles of ECG consult Doyle, 2011). Furthermore, an additional pinch clip at the base of the 3 leads was attached to clothing to prevent the clips from pulling on electrodes and distorting measurements. Data was collected and analysed

using the accompanying Biopac Student Lab Pro software package, and all recordings were taken in milliseconds and at 50 Hz.

4.5.2.4 Signal processing technique

Raw data was processed using BSL Pro, a HRV data analysis software package. Both time and frequency domain measurements were conducted on heart rate data to triangulate findings and increase reliability. Time domain measurements included RMSSD and NN50, and a single frequency measurement was used at high frequency (HF). Noise and movement artefacts were identified and removed using AcqKnowledge, an accompanying data analysis software package of BSL Pro, and HRV averages were collated into text files and analysed using SPSS version 25.

Figure 4.7 – A diagram of Einthoven's Triangle, demonstrating the correct electrode placement on the body to capture a picture of heart activity. In the current study positive (white) is attached below the right collar bone, negative (black) below the left collar bone and earth (red) above the left hip.



4.5.2.5 Strengths and limitations

ECG is non-invasive and affordable with a wide range of research applications. Despite superficial readings of cardio activity, ECG reveals a wealth of information about the rate and rhythm of the heart, which can be used to assess a range of physiological changes in the body (Klabunde, 2011). For instance, despite only capturing echoes of atrial and ventricular muscle activity at the skin and excluding interior measurements, readings of HRV are still possible which index heart reactivity and can provide a picture of cardiac health (Doyle, 2011). Moreover, the physiological signal of ECG is robust to signal

interference such as movement noise, which allows use of the apparatus during exercise and other tasks which require physical activity (Giles, Draper, & Research, 2018), particularly with newer technology which is ambulatory (Jeon, Kim, Jeon, & Lee, 2014). Due to signal strength, movement artefacts and noise can also be identified and easily removed during analysis.

Nevertheless, ECG has several limitations of note. For instance, HRV measurements can be interrupted by talking during the recording process, as speech interrupts the respiratory cycle and can alter the IBI on an ECG trace (Hampton, 2013). Short-term recordings may also be insufficient for determining irregular or differential HRV, and longer measurements may have to be employed to identify heart rate variances. Furthermore, HRV is very sensitive to ectopic beats, and if data is not inspected carefully, uncorrected artefacts may go undetected (Electrophysiology, 1996). Finally, measurements at high exercise intensities can create large amounts of variation on the ECG trace, which make HRV analysis difficult to conduct (Giles et al., 2018).

4.5.3 Blood Pressure Meter

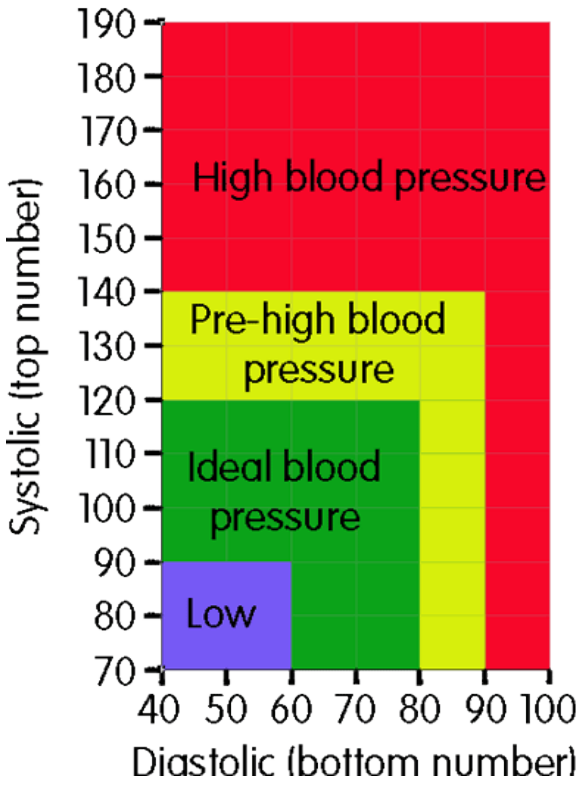
A blood pressure meter (also called a sphygmomanometer), is a device used to record systolic and diastolic blood pressure. The technology works by attaching a cuff around the upper arm which then inflates and collapses, asserting pressure on the artery directly below and constricting blood flow. The pressure applied to the cuff is then slowly released, and blood flow returns to the artery. Depending on the device used (manual or digital) systolic and diastolic blood pressures are recorded differently. In the current research, a digital cuff was used which assesses oscillations in the artery with an in-built pressure sensor. The oscillometric waveform, an algorithm calculated by the device, calculates the mean systolic pressure by estimating when the artery is completely constricted, and

diastolic pressure when it is fully released. Blood pressure is recorded in millimetres of mercury (mmHg), and the meter provides average systolic and diastolic estimates during the period of time in which the artery deflates and refills, but does not provide continuous, real-time measurements (Klabunde, 2011; Kukita, Mitsunami, Aritome, Kato, & Onishi, 2016).

4.5.3.1 Introduction to systolic and diastolic blood pressure

Systolic and diastolic blood pressure indicate the total pressure in blood vessels traveling to and from the heart. Systolic measurements are taken as the heart beats, recording the resulting pressure that carries blood to the arteries from the contracting heart muscles. Diastolic measurements record blood pressure during the interval between beats, when the heart fills with blood prior to muscle contraction. Systolic blood pressure increases when the heart muscles pump blood around the body with greater force, and systolic pressure rises as resistance to that blood flow increases. Optimal blood pressure is displayed in Figure 4.8. An increase in blood pressure is related to an increase in stressful stimuli, and can be used as a physiological indicator of an increase in effort and cognitive workload (Herring & Paterson, 2018).

Figure 4.8 – Chart displaying low to high systolic and diastolic blood pressure readings (mmHg). Higher blood pressure occurs when cardiovascular activity increases.



4.5.3.2 Strengths and limitations

There are various limitations of blood pressure measurements. Primarily, as previously stated, using a standardized arm-cuff method, the meter cannot provide continuous, real-time readings unlike ECG and fNIRS. As such, dynamic changes in blood pressure are difficult to record under laboratory conditions, because readings have to be taken at fixed time points, which may not fully reflect blood pressure fluctuations in all experimental tasks. A further limitation of the meter is the sensitivity in the cuff to arm movement, which can distort the measurement and create false readings. Moreover, digital meters, like the one used in this research, are less precise than manual readers, due to an algorithm that takes estimations, and not exact measurements, of systolic and diastolic blood

pressure. This makes the likelihood of measurement errors higher with digital meters (Shahbabu, Dasgupta, Sarkar, & Sahoo, 2016). Blood pressure readings do, however, have various advantages, particularly concerning the accessibility of the technology. Firstly, the digital meter does not require clinical expertise to use, making it user-friendly to researchers. Additionally, this technology is affordable, and is a popular tool in physiology research. Finally, like ECG, the blood pressure meter can also be used alongside other neurophysiological measures, and as such can be integrated into complex and multi-disciplinary research designs.

4.6 Chapter Summary

This chapter discussed the aims and methodology implemented in the 3 studies which make up this thesis. These aims were derived from peer-reviewed literature and an evaluation of different research methods discussed in the previous chapters. Furthermore, several methods emerged to examine the various research aims, including: a cross-sectional survey; cognitive performance measures; use of fNIRS neuroimaging apparatus; ECG and sphygmomanometer. Close examination of fNIRS by Artinis Medical Systems and use of the CBSI analysis technique revealed that it is an effective neuroimaging technique with strong spatial resolution which can access the DLPFC, a region of the brain strongly associated with cognition. Furthermore, 3-lead Biopac ECG with HF measurements of HRV is a strong means of measuring the heart's reactivity to stress and cognitive workload. Use of a digital sphygmomanometer alongside these methods is another effective tool for indexing physiological reactivity and taken together a neurophysiological measurement of cognitive effort and workload can be obtained. Consequently, what follows are 3 research studies designed to comprehensively examine PCE use. The first study responds to the

previously discussed prevalence estimates which suggest that use of CE, specifically modafinil, is on the rise in UK universities. As such, a cross-university survey investigating the patterns and factors potentially predicting use of CE is discussed in the next chapter. Furthermore, Study 2 and 3 take a closer look at long-term modafinil use on cognition, neurophysiology and psychophysiology to establish what impact the drug has on these functions.

Chapter 5: Study 1 – Investigating Levels of CE use and Predictive Factors Across four UK Universities.

5.1 Chapter Overview

In Chapter 1, CE prevalence rates across Europe and the USA were reviewed and although PCE use was noticeably smaller in Europe than the USA, some data indicated that use of these drugs is on the rise. This chapter describes a study that examined PCE user rates in four UK universities to test the previous claims, and examined the relationship between use and predictive variables, including demographic, and educational factors. The implications of CE use in UK universities are discussed, and these findings also inform the rationale for studies 2 and 3 of the thesis.

5.2 Introduction

Evidence suggests that use of prescription and illegal drugs for the purpose of improved performance during work and while studying is on the rise. Such reports began in the media, where use of PCEs to facilitate academic performance has been estimated to be as high as 10% in some UK universities (Lennard, 2009; The Student Room, 2016). Even so, further examination of these claims reveals that, due to the lack of scientific rigour and robust methods when investigating use, such prevalence estimates may be sensationalised (Partridge, Bell, Lucke, Yeates, & Hall, 2011). Nevertheless, peer-reviewed studies indicate that, although prevalence is not found to be as consistently high as media speculation, it does appear to be on the rise both in the UK and internationally (Maier, Ferris & Winstock, 2018). Still, it is difficult to provide comparable cross-cultural prevalence estimates because of differences in defining CE use and due to variations in how it is measured between

studies (Advokat & Scheithauer, 2013; Emanuel et al., 2013; Maier et al., 2016; Maier & Schaub, 2015; Mazanov, Dunn, Connor, & Fielding, 2013). However, it is clear that CE user rates are generally higher in the USA than Europe. For instance, estimates put non-medical stimulant use in American universities between 5 to 55% (McCabe, West, Teter, & Boyd, 2014; Smith & Farah, 2011), whereas use in Germany appears to be as low as < 1% (Dietz, 2013). Furthermore, in the UK, PCE use appears to be marginally higher than Germany but still below the USA (≤5%) (Holloway & Bennett, 2012; Singh et al., 2014a), though there are relatively few largescale studies.

Notwithstanding limitations of prevalence estimates, available research clearly indicates that use of soft enhancers is considerably more prevalent than that of prescription stimulants and illegal drugs for PCE around the world (Maier et al., 2013; Singh, Bard, & Jackson, 2014b; Wolff, Brand, Baumgarten, Lösel, & Ziegler, 2017). Moreover, when soft enhancer use is disregarded, the next most popular substances are MPH, d-amphetamine and modafinil. In Europe, MPH is the most popular PCE drug used non-medically among university students (Mache, Eickenhorst, Vitzthum, Klapp, & Groneberg, 2012; Maier & Schaub, 2015), and in the USA d-amphetamine is most prevalent (Varga, 2012). Student use of both of these substances is notably low in the UK, although modafinil is shown to be the most commonly used PCE (Maier, Ferris & Winstock, 2018), despite use being limited elsewhere (Maier et al., 2016). Furthermore, respondents who report non-medical PCE use are also more likely to use illegal drugs both recreationally and to enhance study (Maier et al., 2006; McCabe, Boyd & Teter, 2009; McCabe, West, Teter, & Boyd, 2014). For instance, Maier et al. (2016) found that past use of cocaine, amphetamine, cannabis and MDMA were all significant predictors of PCE use and made respondents 6 to 20 times more likely to use prescription stimulants non-medically. Furthermore, a later study by the same group is the most comprehensive examination of international CE use to date, with 100,000 people surveyed across 15 major countries (Maier, Ferris & Winstock, 2018). Respondents

completed the Global Drug Survey (GDS) in 2015 and 2017, and both illegal drug and PCE use was seen to increase in all countries. In the UK alone, illegal stimulant use increased from 1.9% to 13.3%, and PCE use went from 1.7% to 5.1%. Additionally, modafinil use in the UK was the highest among the other countries, and significantly increased from 2015 (3.2%) to 2017 (10%) to be consistent with previous reports by the media. Of course, samples were self-selected meaning that accurate prevalence estimates in the UK and the other countries are not fully known. Nevertheless, rising figures between the two dates indicate growth in non-medical PCE use.

Certain demographic and personality factors have also been found to influence CE use. Many studies reveal gender differences in PCE use, with men most likely to take illicit drugs and PCE both recreationally and for study (Maier et al., 2016; Maier et al., 2018). Age has similarly been linked to use, as over 25s, and more specifically people aged 35 to 44, are found to be more likely to take PCE (Maier et al., 2016; Maier at al., 2018). Furthermore, simply being in higher education is not associated with use but working alongside study on a part-time or full-time basis is (Maier et al., 2016). Additionally, more senior students, such as undergraduates in their final year and those in postgraduate study, have been shown to be more likely to use illicit drugs and PCE than junior undergraduates (Maier et al., 2013). An assessment of attitudes toward PCE use has also found that moral perceptions of use, examined through fictional vignettes, are linked to consumption, with respondents who believe that use is morally acceptable more likely to be users or consider use (Maier, Liakoni, et al., 2015). Finally, it has been demonstrated that higher levels of academic stress are related to PCE use (Maier et al., 2013), but studies have failed to assess whether consumption is similarly related to various factors which might contribute to this stress.

Therefore, the aim of the current study was to fully explore CE use in 4 universities across the UK. A survey study has yet to be conducted in the UK which investigates levels of CE

use and factors which predict use concurrently. Consequently, this survey examines factors which previous studies have shown to be related to CE use (i.e., gender, age, moral perceptions, employment status and year of study) and those that have yet to be explored. Academic stress has been linked to PCE use, but factors which might underlie such pressure have not. For instance, semester-time accommodation (whether a student lives with parents or is self-supported) and gross annual income are variables which may add to university stress, as either of these factors could feasibly limit time or access to study resources. Furthermore, academic performance, learning styles (whether a student takes a surface or deep learning approach) and academic self-efficacy may also successfully predict PCE use. Prior research has already linked low academic performance and academic self-efficacy to substance abuse (Meier, Hill, Small, & Luthar, 2015; Smorti, 2014; Welsh, Shentu, & Sarvey, 2019), and while the same is not true of learning styles, it is also feasible that less successful study strategies (i.e., a surface learning approach) could be linked to CE use as a method of compensation. As such, these variables were also explored in order to address several hypotheses. First, it was predicted that use of soft enhancers would be higher than PCE regardless of user intent (H^1). Second, it was predicted that modafinil would be the most popular PCE drug for study purposes (H^2). Third, reported use of illegal drugs for study would be smaller than soft enhancers and PCE, but recreational use would be higher than PCE (H^3). Finally, sociodemographic and personality factors would predict use. Specifically: Gender (being male), age (being older), level of study (being postgraduate), learning styles (being a surface learner) and moral perceptions of PCE use (H^4).

5.3 Method

5.3.1 Participants

Data was collected from January 2016 to September 2017. An opportunity sampling method was used with snowball sampling and 750 university students responded to the survey from across four UK universities: Northwest 1 (NW1), Northwest 2 (NW2), East Midlands 1 (EM1) and Northeast 1 (NE1). In total, 389 respondents completed all measures and were included in analysis. However, response rates varied substantially between academic institutions (NW1: *N* = 256, NW2: *N* = 71) making cross-university statistical analysis unviable. As such, samples were combined into a single set. On average, participants were 22 years old (SD = 4), and more females completed all sections of the survey than males (females = 70.31%). Age was also similar between CE user groups (nonusers = mean: 21, SD: 5; soft enhancer users = mean: 22, SD: 4; illicit drug users = mean: 23, SD: 6 PCE users = mean: 22, SD: 3), and groups were predominantly female (female users = nonusers: 80%, soft enhancers: 77%, illicit drugs 81%), except in the case of PCE users (male users = PCE: 57%).

5.3.2 Design

The current study was an exploratory between-groups cross-sectional survey with a mixed design used to measure respondent data. The first between-groups factor was CE user group which had 4 levels (nonusers; soft enhancer users; soft enhancer and illicit drug users; and soft enhancer, illicit drug and PCE users, hereafter entitled: nonusers, soft enhancer users, illicit drug users and PCE users). The second between-groups factor was type of use with 2 levels (recreational vs. study). Furthermore, there were 2 dependent

variables for analysis concerning levels of CE use (lifetime use and previous year use). Finally, several additional variables examined sociodemographic and educational status to assess their impact on CE use, including: age, gender, term-time accommodation, level of study, employment statuses, semester time address, mode of study, annual income, UCAS points, moral perception, academic self-efficacy and learning style (see Data Analysis Strategy for further details).

5.3.3 Materials

Participants completed the Cognitive Enhancement Use Survey along with the Academic Self-Efficacy Scale, the R-SPQ-2F and the CE-MJT. The survey was hosted on Qualtrics Software by Qualtrics Software Company (Seattle, Washington), an online survey platform. Participants completed the anonymous survey via a link which was compatible with their personal computer or mobile and tablet devices. Data was then downloaded in Microsoft Word document format and transferred to an SPSS spreadsheet for analysis.

5.3.3.1 Cognitive Enhancement Use Survey

To investigate patterns of CE use at UK universities, a comprehensive survey was created which examines use of a wide inventory of CE related drugs. The questionnaire was divided into sections which appeared in randomised order to reduce order effects and examined sample demographics and patterns of CE use.

i) Demographics.

Respondents were asked about their: age, gender (A. Male, B. Female, C. Transgender), maximum level of academic achievement (A. Foundation degree, B. First year undergraduate, C. Second year undergraduate, D. Third year undergraduate, E. Master's

degree, PGCERT, PGDIP, F. PhD or professional doctorate), study status (A. Full-time student, B. Part-time student), employment status (A. Unemployed, B. Part-time employed, C. Full-time employed) and term time accommodation (A. Student accommodation, B. Privately rent, C. Live with parents/guardian, D. Other). Participants were also asked for estimates of gross annual income and UCAS points upon entry to university.

ii) Levels of CE Use.

Use of different psychoactive substances is also investigated, including: alcohol and illegal drugs (amphetamine, cocaine and cannabis); PCEs (d-amphetamine, MPH, modafinil and piracetam); caffeine based soft enhancers (coffee, caffeine pills, energy drinks and guarana); and herbal-based (nutraceutical) soft enhancers (ginseng, gingko biloba, citicoline, galantamine and bacopa monniera). Use is recorded for: lifetime (study aid or recreationally), previous year (study aid or recreationally), and number of occasions used in a month (typical month and month prior to an exam). Circumstances of use are also assessed, including: route of administration (A. swallowed, B. Smoked, C. Snorted, D. Injected); acquisition (A. Internet, B. Drug Dealer, C. Friend, D. Family member, E. Retailer, F. Prescription), and difficulty of acquisition (presented on a 5-point Likert scale: 1 = very easy, 5 = very difficult).

5.3.3.2 The Academic Self-Efficacy Scale

The Academic Self-Efficacy Scale is a 10-item scale investigating academic self-efficacy, which is characterised as a person's belief in their academic performance (McIlroy, Poole, Ursavas & Moriarty, 2015). Each item is scored on a 7-point Likert scale (1 = very strongly disagree, 7 = very strongly agree). Questions 5, 6 and 9 are reverse scored and a total score is calculated by adding the sum of all answered questions together (range from 7 to 70) and higher scores indicate greater academic self-efficacy. Questions include items such as 'If I

don't understand an academic problem, I persevere until I do' and 'No matter how hard I try, I can't seem to come to terms with many of the issues in my academic curriculum' (reverse scored). Reliability analysis with data from this study shows strong internal consistency (α = .733).

5.3.3.3 The Revised Study Process Questionnaire (R-SPQ-2F)

The R-SPQ-2F is a 20-item questionnaire which assesses learning styles. Questions are presented on a 5-point Likert scale (A = always true of me, E = never true of me). Items are presented as statements, such as; 'I find that at times studying gives me a feeling of deep personal satisfaction' and (reverse scored) 'My aim is to pass the course while doing as little work as possible'. Respondents are categorised across 4 dimensions (A. Deep motive, B. deep strategy, C. surface motive D. surface strategy). Five items are dedicated to each dimension and the questionnaire is scored by converting responses into numbers (A = 5, E = 1 and inverted for reverse items), which provides an individual score for each dimension. Higher scores on the deep motive and deep strategy dimensions indicate a deep approach to learning, whereas similar scores on the surface motive and surface strategy dimensions signify a surface learning style. A score of 25 across any of the 4 facets suggests the highest possible preference toward that learning approach (Biggs, Kember & Leung, 2001).

5.3.3.4 Cognitive Enhancement Moral Judgment Test (CE-MJT)

The CE-MJT is a 22-item PCE moral judgement scale based on the Moral Judgement Test (MJT), which assesses moral judgement competence (Lind, 2013). This scale focuses on PCE use specifically and is similar in structure to the MJT. The CE-MJT is divided into three sections, examining moral attitudes towards: MPH, modafinil and d-amphetamine use. Each section opens with a short story detailing a moral conundrum which concerns the use

of a PCE drug at university. There are 7 items in each section presented on a 7-point Likert scale (1 = strongly disagree, 7 = strongly agree). Each section is tallied individually and total scores range from 7 to 49, though certain items are reverse scored (Sally: 3, 4, 7; Simon: 1, 2, 4, 5, 7; John: 2, 4, 6, 7). A higher score indicates greater moral acceptability toward each PCE drug, and a composite score can be obtained by adding the scores from the 3 vignettes together. Questions are presented as statements, such as standard questions; 'It doesn't matter what techniques Sally uses to study only that she gets good grades' and 'Simon is wrong to have used Adderall for so long during his studies' (reverse scored). A final question at the end of the test also asks participants 'How difficult was it to answer these questions?' Moreover, reliability tests with the data revealed that each subscale of the CE-MJT was internally consistent (d-amphetamine vignette: α = .833, modafinil vignette: .844, α = MPH vignette: α = .897) (See Appendix for full test).

5.3.4 Procedure

The study was approved by Liverpool John Moores University Research Ethics Committee in January 2016 and received gatekeeper approval from the other three participating institutions. Gatekeepers at each university promoted the study to their student cohort. Participants were contacted through institutional email lists and were sent a recruitment email detailing the aims and participant information for the study. A digital copy of the participant information sheet (PIS) was also included and the recruitment email had a URL to the online survey which was hosted on a secure Qualtrics server. After providing consent, participants began the cognitive enhancement use survey, a questionnaire comprised of 4 sections assessing: patterns of CE use, learning styles, academic self-efficacy, and moral judgement. The presentation of each section of the survey was randomized, to reduce order effects and response bias. At the end of the survey,

participants were given the opportunity to provide an email address to be entered into a prize draw for a £50 retail voucher.

5.3.6 Data Analysis Strategy

Data was downloaded from the Qualtrics server and cleaned using IBM's Statistical Package for the Social Sciences (SPSS) Version 25. A single period of use or more of drugs belonging to any of the user group categories (nonuser, soft enhancer user, illicit drug user and PCE user) was enough to be assigned to that CE group. Unfortunately, due to limitations imposed by total responses to the survey, it was not possible to create groups of respondents who exclusively used only one category of drug (e.g., only PCE and no other substances), as such, some respondents used substances from multiple categories. In addition to descriptive statistics used to investigate sample characteristics, Chi square analysis was used to examine differences in levels of use between user groups and between recreational and study use with the individual drugs belonging to each category (e.g., PCE: modafinil, MPH, d-amphetamine and piracetam). Furthermore, mixed ANOVA assessed user group differences in response to the moral vignettes (i.e., modafinil vignette, MPH vignette and d-amphetamine vignette), while between-groups ANOVA examined differences in users on the Academic Self-Efficacy Scale. Multivariate analysis of variance (MANOVA) was also used to analyse differences between user group categories on learning styles reported on the R-SPQ-2F (i.e, deep motive, surface motive, deep strategy and surface strategy learning styles). Finally, a multinomial logistic regression was conducted to identify predictors of CE use. Various categories for predictor variables were combined to strengthen regression analysis, including year of study (undergraduate or postgraduate), employment status (employed or unemployed) and term-time accommodation (living with or away from parents). Variables were entered or excluded from the model based on

whether they showed significance in several ANOVA with the different user groups as the IV. Previous research in the area did not indicate a consistent order of importance to CE use so a forced entry method was used. Furthermore, Mode of study, annual income, and UCAS points were excluded from regression analysis because of inadequate response rates to those questions in some CE user groups.

5.4 Results

5.4.1 Sample Demographics

Demographic and educational information for each group is presented in Table 5.1. Multiple 2 x 4 chi-square cross-tabulations were used to compare user groups on the various demographic variables. Unfortunately, due to insufficient responses in the illicit drug users' group (n = 0), gross annual income could not be assessed, but all other demographic variables were included in analysis. Overall, there were more females (X^2 (2, N = 389) = 32.74, $p < .001$) in the non-user, soft enhancer, and illicit drug groups. However, there were more male PCE users than female (male users = PCE: 57%). There was no significant differences between full-time or part-time study (X^2 (1, N = 389) = 3.03, $p > .05$), current year of study (X^2 (1, N = 389) = 21.15, $p > .05$) employment status (X^2 (1, N = 389) = 3.85, $p > .05$) or semester-time accommodation (X^2 (1, N = 389) = 7.47, $p > .05$) on lifetime CE use. A between-groups analysis showed that age ($F(3, 376) = .62$, $p > .05$, $\eta_p^2 = .013$) and UCAS points on entry to university ($F(3, 219) = 1.55$, $p > .05$, $\eta_p^2 = .011$), did not significantly differ between the user groups.

Table 5.1 –Demographic and educational information in respondents who completed all sections of the survey.

	Nonusers		**Soft Enhancers**		**Illicit Drugs**		**PCE**		**Total**	
		N		***N***		***N***		***N***		***N***
					Mean (SD)					
Age	21.73 (2.08)	*120*	22.04 (4.73)	*215*	23.44 (6.12)	*18*	22.27 (3.18)	*26*	22.02 (4.81)	*379*
UCAS	324.99 (89.97)	*72*	315.80 (96.64)	*122*	251.63 (80.89)	*10*	315.47 (55.00)	*17*	316.46 (91.82)	*219*
Gender					%					
Female	80.00%	*100*	77.47%	*172*	81.25%	*13*	40.00%	*10*	76.03%	*295*
Male	20.00%	*25*	22.52%	*50*	18.75%	*3*	60.00%	*15*	23.96%	*93*
Study Year					%					
Undergraduate	80.08%	*101*	76.57%	*170*	87.05%	*14*	69.23%	*18*	77.89%	*303*
Postgraduate	19.02%	*24*	23.42%	*52*	12.05%	*2*	30.76%	*8*	22.10%	*86*
Study Status					%					
Full-time	96.74%	*119*	97.74%	*217*	100%	*16*	92.30%	*24*	97.15%	*376*
Part-time	3.25%	*4*	2.25%	*5*	0%	*0*	7.69%	*2*	2.84%	*11*
Employment Status					%					
Unemployed	59.19%	*74*	55.40%	*123*	43.75%	*7*	69.23%	*18*	57.06%	*222*
Employed	40.08%	*51*	44.59%	*99*	56.25%	*9*	30.76%	*8*	42.93%	*167*
Semester Residence					%					
Student/Private Residence	77.41%	*96*	80.18%	*178*	81.25%	*13*	80.79%	*21*	79.38%	*308*
Parental/Guardian Residence	22.58	*28*	19.81%	*44*	18.75%	*3*	19.23%	*5*	20.61%	*80*

5.4.2 Patterns of Use

Lifetime and previous year use of CE substances for study and recreation are presented in Table 5.2. Regardless of intent, use of soft enhancers was highest across lifetime, followed by illicit drugs then PCE. Additionally, use was greater recreationally than for study purposes with soft enhancer and illicit drugs, but not for PCEs which saw marginally higher use as a study aid. Levels of use fell in the previous year, but maintained a similar trend, except for recreational use of illicit drugs and PCE's which were markedly smaller than general lifetime use.

Table 5.2 – Lifetime and previous year use of soft enhancers, illicit drugs and PCE for recreational and study purposes. Expected values for one-sample chi-square are recorded here.

	N (%)					
Institution	**Study Soft**	**Recreational Soft**	**Study Illicit**	**Recreational Illicit**	**Study PCE**	**Recreational PCE**
Lifetime Total	261 (67.09%)	341 (87.66%)	24 (6.16%)	161 (41.38%)	26 (6.68%)	22 (5.65%)
Expected Value (*E*)	80.21		31.13		32.26	
Previous Year Total	239 (61.43%)	333 (85.60%)	18 (4.62%)	110 (28.27%)	22 (5.65%)	11 (2.82%)

Note: Abbreviations: Soft, soft enhancer; Recreational, recreational use.

One-sample chi-square analysis showed that significantly more respondents had used soft enhancers recreationally than for study in their lifetime (X^2 (1, N = 389) = 73.92, $p < .05$) (See Table 5.3). Caffeinated products were those used most widely for study, while alcohol was the most popular drug recreationally. However, noticeably fewer people reported using alcohol as a study aid, although this was still more than reported levels of the

nutraceutical substances. Nonetheless, more people reported using nutraceuticals recreationally, but this was still comparatively lower than caffeinated products and alcohol. Moreover, levels of use in the previous year were marginally smaller but similar for most soft enhancers, except for nutraceuticals which were noticeably smaller both for study and recreational use, suggesting extremely limited use of these substances within the sample.

Table 5.3 – Lifetime and previous year use of drugs categorised as soft enhancers for recreational or study purposes.

	Lifetime N (%)		**Previous Year N (%)**	
	Study	**Recreation**	**Study**	**Recreation**
Alcohol	31 (7.96%)	320 (82.26%)	22 (5.65%)	310 (79.69%)
Bacopa Monniera	6 (1.54%)	13 (3.34%)	2 (0.51%)	5 (1.28%)
Caffeine Pills	70 (17.99%)	64 (16.45%)	47 (12.08%)	37 (9.51%)
Citicoline	5 (1.28%)	11 (2.82%)	3 (0.77%)	6 (1.54%)
Coffee	194 (49.87%)	218 (56.04%)	186 (47.81%)	213 (54.75%)
Energy Drinks	167 (42.93%)	189 (48.58%)	132 (33.93%)	166 (42.67%)
Ginseng	26 (6.68%)	42 (10.79%)	11 (2.82%)	23 (5.91%)
Ginkgo Biloba	14 (3.59%)	19 (4.88%)	6 (1.54%)	5 (1.28%)
Guarana	12 (3.08%)	27 (6.94%)	6 (1.54%)	12 (3.08%)
Tobacca	43 (11.05%)	150 (38.56%)	36 (9.25%)	118 (30.33%)

Lifetime and previous year illicit drug use is presented in Table 5.4. One-sample chi-square analysis revealed that significantly more respondents used illicit drugs for recreational purposes than for study (X^2 (1, N = 389) = 36.22, p < .001). Cannabis was the most used drug across the lifetime and in the last year, and this was predominantly for recreation. The same was true for cocaine and amphetamine, although reports of use were lower compared with the other drugs.

Table 5.4 – Lifetime use of drugs categorised as illicit substances for recreational or study purposes.

	Lifetime N (%)		**Previous Year N (%)**	
	Study	**Recreation**	**Study**	**Recreation**
Amphetamine	7 (1.79%)	30 (7.71%)	3 (0.77%)	13 (3.34%)
Cannabis	18 (4.62%)	158 (40.61%)	11 (2.82%)	104 (26.73)
Cocaine	8 (2.05%)	65 (16.70%)	6 (1.54%)	42 (10.79%)

Lifetime and previous year use of PCE drugs is presented in Table 5.5. A one-sample chi-square test revealed that lifetime PCE use was also significantly more likely to be for recreational than for study purposes (X^2 (1, N = 389) = 56.20, p < .001). However, patterns of use were not as consistent as with the other categories. Lifetime estimates revealed that, recreationally, d-amphetamine was the most used substance, but for study, modafinil was most popular. Methylphenidate had similar levels of use for recreation and study, and piracetam was the most uncommonly used drug in both categories. In the previous year, d-amphetamine and modafinil were the most used recreational substances, and their use was only marginally smaller for study. Modafinil remained the most popular study drug, despite being markedly less common for recreational use, and piracetam was again the

most unpopular across categories. As such, PCE use was generally rare when compared with soft enhancers and illicit drugs, and patterns of use were less consistent.

Table 5.5 – Lifetime and previous year use of PCE drugs for recreational or study purposes.

	Lifetime N (%)		**Previous Year N (%)**	
	Study	**Recreation**	**Study**	**Recreation**
D-Amphetamine	8 (1.28%)	12 (3.08%)	6 (1.54%)	7 (1.79%)
MPH	10 (2.57%)	11 (2.82%)	6 (1.54%)	7 (1.79%)
Modafinil	19 (4.88%)	9 (2.31%)	15 (3.85%)	4 (2.31%)
Piracetam	3 (0.77%)	7 (1.79%)	1 (0.25%)	3 (0.77%)

5.3 CE User Group Comparisons

Data on moral judgements, learning strategies and academic self-efficacy are presented in Table 5.6. Mixed ANOVA was conducted on user group responses to the 3 moral judgement vignettes (within group analysis: d-amphetamine vignette, MPH vignette, modafinil vignette). The assumption of sphericity was not met ($p < .05$), and therefore homogeneity could not be assumed. As such, the Greenhouse-Geisser correction was used to report effects. There was a highly significant main effect of vignette on moral judgement, ($F(1.89, 379) = 62.43$, $p < .001$, $\eta_p^2 = .933$). Contrasts revealed a linear trend, in that respondents believed John's MPH use was less morally acceptable than Sally's modafinil use, and her use less acceptable than Simon's use of d-amphetamine, ($F(1, 379) = 27.13$ $p < .05$, $\eta_p^2 =$

.719). However, the interaction between vignettes and user groups was non-significant ($F(5.69, 379) = 1.11$, $p > .05$, $\eta_p^2 = .027$). Nevertheless, follow-up one-way ANOVA did reveal that there were significant differences between user groups on the MPH vignette ($F(3, 385) = 8.53$, $p < .001$, $\eta_p^2 = .636$), d-amphetamine vignette ($F(3, 384) = 8.54$, $p < .001$, $\eta_p^2 = .670$) and modafinil vignette ($F(3, 384) = 10.64$, $p < .001$, $\eta_p^2 = .601$). Further post-hoc Bonferroni analysis showed that PCE users found the use of all 3 substances significantly more morally justifiable than the other groups. Moreover, between groups analysis showed that there was no significant difference between user groups and how morally challenging participants found the questions ($F(3, 388) = 1.29$, $p > .05$, $\eta_p^2 = .081$).

Multivariate analysis of variance was conducted to assess user group differences in learning strategies. Findings indicated that there were no significant user group differences across the four learning styles ($F(3, 348) = .653$, $p > .05$, $\eta_p^2 = .004$) suggesting that that regardless of CE use, respondents had similar approaches to learning. Between-groups ANOVA was also used to compare the groups on academic self-efficacy and perceptions of risks and benefits of CE use. This showed that CE user groups did not significantly differ on either academic self-efficacy ($F(3, 361) = 1.43$, $p > .05$, $\eta_p^2 = .011$) or risk perceptions ($F(3, 361) = .675$, $p > .05$ $\eta_p^2 = .001$).

Table 5.6 – Showing CE user group scores across the behavioural measures: academic self-efficacy, learning styles and moral judgements.

	Nonusers		S. Enhancers		Illicit Drugs		PCE		Total	
	Mean (SD)									
	N =									
Academic Self-Efficacy	30.57 (7.75)	*108*	30.03 (7.75)	*215*	31.80 (10.54)	*16*	33.25 (8.86)	*24*	30.48 (7.68)	*362*
Deep Motive Learning	16.15 (3.68)	*101*	16.18 (4.00)	*211*	15.76 (3.96)	*13*	16.16 (4.32)	*24*	16.15 (3.91)	*349*
Deep Strategy Learning	15.76 (3.56)	*101*	15.82 (3.93)	*211*	15.07 (4.07)	*13*	15.54 (3.48)	*24*	15.76 (3.79)	*349*
Surface Motive Learning	19.10 (3.94)	*101*	19.03 (4.08)	*211*	17.76 (3.46)	*13*	17.20 (4.10)	*24*	18.88 (4.04)	*349*
Surface Strategy Learning	15.98 (3.01)	*101*	16.00 (3.12)	*211*	15.69 (3.94)	*13*	15.87 (2.21)	*25*	15.97 (3.06)	*349*
MPH Vignette	22.60 (8.42)	*123*	23.42 (8.48)	*218*	29.50 (8.27)	*16*	30.26 (5.84)	*26*	23.87 (8.55)	*383*
D-Amphetamine Vignette	28.41 (9.80)	*123*	29.69 (9.39)	*218*	35.06 (9.69)	*16*	38.88 (7.20)	*26*	30.13 (9.75)	*383*
Modafinil Vignette	24.47 (8.12)	*123*	26.31 (8.77)	*218*	31.56 (9.20)	*16*	35.65 (8.32)	*26*	26.57 (8.99)	*383*

Note: Abbreviations S. Enhancers, soft enhancers; SD, standard deviation.

5.4.4 Multinomial Logistic Regression

Univariate ANOVA and chi-square cross tabulations were used as screening analysis to assess the suitability of the different factors for predicting soft enhancer, illicit drug and

PCE use in the logistic model. With ANOVA, significant main effects were found for age (F(3, 359) = 3.250, p < .05, η_p^2 = .127) the modafinil moral vignette (F(3, 387) = 14.245, p < .001, η_p^2 = .610), d-amphetamine moral vignette (F(3, 385) = 8.543, p < .001, η_p^2 = .263) and MPH moral vignette (F(3, 384) = 10.649, p < .001, η_p^2 = .277). No significant main effects were observed for academic self-efficacy (F(3, 361) = 1.437, p > .05, η_p^2 = .012), or any of the learning styles (surface strategy: F(3, 361) = .025, p > .05, η_p^2 = .000; deep strategy: F(3, 360) = .038, p > .05, η_p^2 = .002; surface motive: F(3, 363) = 1.810, p > .05, η_p^2 = .015; deep motive: F(3, 362) = .009, p > .05, η_p^2 = .000). For chi-square analysis, there was a significant association of gender (X^2(3) = 19.384, p < .001), but all other cross tabulations were non-significant (study level: X^2(3) = 2.827, p > .05; employment status: X^2(3) = 3.211, p > .05; semester time residence: X^2(3) = .443, p > .05). Consequently, the H^4 could not be fully supported as not all variables posited significantly differed across user groups. As such, all remaining predictor variables with significant main effects were run in the regression model.

Multinomial logistic regression was used to investigate the possible predictor variables associated with the different CE user groups. Each CE group (soft enhancer, illicit and PCE user) was compared against nonusers throughout analysis. The model was highly statistically significant (X^2(15) = 63.745, p < .001). Beta values, odds ratios and upper and lower confidence intervals for the different CE user groups are presented in Table 5.7. Age significantly predicted soft enhancer use (b = .186, Wald X^2(1) = 4.128, p < .05) in that being older was associated with greater use. Responses to the modafinil moral vignette also significantly predicted soft enhancer use (b = .061, Wald X^2(1) = 4.605, p < .05.). Furthermore, odds ratios indicate that respondents were more likely to use soft enhancers for study the more they believed modafinil use to be morally justifiable. However, gender (b = -.162, Wald X^2(1) = .265, p > .05.), perceptions of d-amphetamine (b = -.004, Wald X^2(1) = .021, p > .05.) and MPH (b = -.016, Wald X^2(1) = .623, p > .05.) use were not significant

predictors of soft enhancer use. With illicit drugs for study, age was found to be the only significant predictor variable (b = .186, Wald $X^2(1) = 4.433$, $p < .05$), although responses to the modafinil moral judgement vignette showed a statistical trend (b = .2.987, Wald $X^2(1) = 3.226$, $p = .090$). Gender (b = .627, Wald $X^2(1) = .695$, $p > .05$), perceptions of d-amphetamine (b = .068, Wald $X^2(1) = 2.123$, $p > .05$) and MPH (b = .015, Wald $X^2(1) = .076$, $p > .05$) use did not significantly predict illicit substance use. For PCE use, age was also a significant predictor (b = .152, Wald $X^2(1) = 3.622$, $p < .05$.) again being associated with older users. Gender was also a significant predictor, (b = -1.199, Wald $X^2(1) = 5.210$, $p < .05$, with males more likely to use PCE than females. Responses to the modafinil moral vignette also significantly predicted PCE use (b = .099, Wald $X^2(1) = 4.610$, $p < .05$.) with confidence intervals revealing that respondents were more likely to use PCE for study if they believed modafinil use was more morally justifiable. Both perceptions of d-amphetamine (b = .023, Wald $X^2(1) = .355$, $p > .05$.) and MPH (b = .045, Wald $X^2(1) = .866$, $p > .05$.) did not significantly predict PCE use.

Table 5.7 – Beta values, odds ratios and confidence intervals of predictor variables as they relate to soft enhancer, illicit drug and PCE use.

	B(*SE*)			**Lower**			**Odds Ratio**			**Upper**			***N***
	Soft Enhancer	Illicit Drugs	PCE	Soft Enhancers	Illicit Drugs	PCE	Soft Enhancers	Illicit Drugs	PCE	Soft Enhancers	Illicit Drugs	PCE	
Age	**.096(.047)***	**.186(.088)***	**.152(.080)***	1.003	1.013	.995	1.101	1.205	1.164	1.207	1.432	1.362	360
Gender	-.162(.314)	.627(.752)	**-1.199(.525)***	.460	.429	.108	.851	1.871	.301	1.574	8.170	.844	388 (male: 93)
Moral Vignette: modafinil	**.047(.025)***	.083(.054)	**.099(.046)***	.999	.978	1.009	1.049	1.087	1.104	1.100	1.207	1.209	388
Moral Vignette: d-amphetamine	-.004(.021)	.068(.047)	.023(.038)	.957	.977	.949	.996	1.070	1.023	1.037	1.173	1.103	386
Moral Vignette: methylphenidate	-.016(.021)	.015(.053)	.045(.048)	.944	.915	.952	.984	1.015	1.046	1.025	1.125	1.150	385
N	222	16	26										

Note: R^2 = .165 (Cox & Snell), .191 (Nagelkerke). Model X^2 (15) = 63.745, significant at .05*

5.5 Discussion

Findings from this survey support most hypotheses outlined for study 1. As expected, soft enhancers were used more than PCE and illegal drugs regardless of user intent. Soft enhancers were also the most frequently reported class of drugs used as a study aid, followed by PCE and illegal drugs. Additionally, modafinil was the most popular PCE drug for study purposes, with levels of use in the sample similar to those reported in previous research. Moreover, recreational past year PCE use was much lower than soft enhancers and illicit drugs, but for study, rates were similar to illicit drugs. Furthermore, the statistical model significantly predicted CE use, as did several individual predictor variables. Respondents were more likely to use all categories of CE if they were older. Greater belief in modafinil use being morally acceptable also significantly predicted soft enhancer and PCE use, and being male was associated with PCE use. Finally, all other factors failed to predict CE use individually. As a result, the H^1, H^2, H^3 were accepted, but as not all sociodemographic factors predicted use, the H^4 was not.

Levels of CE use among the sample were similar to what has previously been reported in Europe and the UK. The proportion of respondents who used soft enhancers recreationally and for study was substantially higher than what is reported with PCE and illegal drugs, perhaps owing to the popularity and general availability of these substances over prohibited and more novel drugs. Moreover, as discussed in Chapter 1 and in the introduction to this chapter, levels of PCE use in the UK are generally low anyway, with many estimates of use equal to or below 5% (Holloway & Bennett, 2012; Singh et al., 2014a). However, despite data being collected during the same time period, this is markedly lower than figures presented by Maier, Ferrins and Winstock (2018) which suggested that recent use, particularly for modafinil, was closer to media reports (Lennard, 2009; The Student Room, 2016). Of course, as already observed, Maier and colleagues'

sample was self-selected, and as a consequence it cannot be used as a true representation of prevalence. Furthermore, other studies have yet to report similar levels of PCE use in the UK, which suggests that level of use may be low.

One of the most important findings to emerge from this survey was the popularity of modafinil above other PCE. Furthermore, moral perceptions of modafinil use significantly predicted soft enhancer and PCE use. Not only does this support evidence that modafinil is the most popular PCE in the UK as it was viewed as the most morally acceptable, but it raises the question of whether or not a pro-moral stance toward the drug leads to use. As such, future research should expand on the relationship between moral perceptions and modafinil use, possibly via moderation analysis. Furthermore, studies should also focus on factors which may predict use more specifically and give greater emphasis to personality measures which research has already linked to PCE use (Maier et al., 2015).

5.6. Chapter Summary

This chapter set out to investigate a sparsely researched area in the UK. Only a handful of studies have examined CE use in British universities, and this survey was the first UK-only study to investigate factors which could predict use. As expected, soft enhancers, particularly those containing caffeine, were by far the most reported for the purpose of study, with illegal drugs and PCE used considerably less for all purposes. Nonetheless, as anticipated, modafinil emerged as the most popular PCE substance among respondents, which is consistent with recent findings in previous research. Moreover, the statistical model successfully predicted CE use, as being older, male and having a favourable opinion of modafinil use were all significant predictors. Consequently, despite PCE use still being limited in the UK and elsewhere, there is sufficient evidence from this survey and previous studies to suggest that modafinil use is on the rise in UK universities, and as such, the drug warrants further investigation. Furthermore, little is understood about persistent use of

this substance in terms of its potential to adversely affect cognition and neurophysiology. As such, Chapters 6 and 7 explore cognitive, psychophysiological and neurophysiological functioning with long-term nonmedical use.

Chapter 6: Study 2 – Differences in Cognitive Performance between Modafinil Users and Non-using Controls.

6.1 Chapter Overview

The previous chapter looked broadly at levels of CE use and associated factors in UK universities, and identified the novel stimulant modafinil as the most popular PCE. Following on from this discovery, this chapter describes a study which examines executive functioning in long-term modafinil users and non-using controls, with the aim to assess whether or not continued use of this drug adversely effects various cognitive functions. Additionally, Chapter 2 demonstrated that response inhibition, working memory and sustained attention were improved with acute modafinil, as such a Go/No-go test, *2*-back working memory task and continuous performance task were used to assess the impact of long-term use.

6.2 Introduction

Previous chapters have demonstrated that modafinil appears to be the most popular PCE among students in the UK, and Study 1 further supported these findings. Furthermore, modafinil has been shown to benefit cognitive processes in healthy and clinical populations (Minzenberg & Carter, 2008). Acute administration studies have highlighted the drug's potential to improve functions in several cognitive domains, including working memory, attention and other processes associated with the prefrontal cortex (Battleday & Brem, 2016). Furthermore, studies assessing dose-dependent effects have found that similar benefits can be conferred from low (100mg) and high doses (600mg), with the greatest advantages being given to healthy but sleep deprived adults (Minzenberg & Carter, 2008).

Additionally, in terms of cognitive benefits, research shows that even small doses are comparable to 600mg of caffeine and 20mg of d-amphetamine, suggesting that in clinically recommended quantities the drug is an effective stimulant (Wesensten et al., 2005). Moreover, modafinil has even been found to reverse working memory deficits and other cognitive functions in psychiatric and ADHD populations, bringing performance in-line with healthy controls (Turner et al., 2004). Nonetheless, studies examining modafinil use in healthy, non-sleep deprived adults have shown equivocal findings, although benefits have been found in various domains, including; attentional and working memory processes without a speed/accuracy trade-off (Müller et al., 2004; Müller et al., 2013), inhibitory control (Rycroft et al., 2007; Turner et al., 2003) and alertness and sustained attention (Baranski et al., 2004; Randall & Shneerson, 2005; Randall et al., 2005) (see Chapter 2 for full review).

Despite these studies showing some benefits to cognition, research does not appear to have investigated the impact of the drug on cognitive performance with prolonged use (3 months and above). Furthermore, at the time of writing, studies have not assessed whether using modafinil against medical guidelines (i.e., not for prescribed purposes) for this period of time could cause adverse effects in the brain and to cognitive function, even if previous studies show the drug is well tolerated with short-term use (see Chapter 2). While studies indicate that in healthy people, working memory, response inhibition and sustained attention are the executive functions most facilitated by use, it is unclear for how long these benefits are sustained, and if after the psychoactive effects of the drug expire cognitive deficits are apparent. It is feasible that, like illegal stimulants, continued nonmedical use of modafinil is neurotoxic (Gawin & Ellinwood, 1988), given the neurochemical similarities the drug has as a dopamine reuptake inhibitor to cocaine (Zolkowska et al., 2009). Therefore, like cocaine, this could lead to persistent cognitive deficits in certain domains, particularly those which show improvement during acute use.

As such, this study sought to investigate cognitive performance in long-term modafinil users who have been abstinent for at least 48 hours, a period of time sufficient to fully deplete the psychoactive effects of the drug based on an elimination half-life of 9 to 14 hours (McClellan & Spencer, 1998). Participants completed a *2*-back working memory task, a go/no-go task (response inhibition) and the continuous performance task (sustained attention) to ascertain whether or not long-term modafinil use leads to deficits in these areas, and to address various hypotheses. Modafinil users would perform significantly worse on cognitive performance measures than nonusers (H^5). More frequent modafinil use would also predict poorer performance on the cognitive performance measures, as would greater poly-drug use and recent use of illicit stimulants and cannabis (H^6). Lastly, it was also anticipated that modafinil use would be significantly correlated with greater levels of poly-drug use reported by participants in the modified Background Drug Use Questionnaire (H^7).

6.3 Method

6.3.1 Participants

Data collection occurred between January 2017 and February 2018. Fifteen modafinil users (mean age = 24.80, SD = 3.48, males = 83.33%) and 18 non-using controls (mean age = 25.72, SD = 3.93 males = 47.77%) participated in the study, with opportunity and snowball sampling methods used for recruitment. Furthermore, participants were contacted through university mailing lists and on speciality online PCE user forums. To be considered a modafinil user, participants had to report using the drug for at least 12 months and on average at least once a month, while nonusers had to have no history of modafinil use, although 'other' drug use was permitted.

6.3.2 Design

A mixed design was implemented to examine behavioural data. The between-groups factor was user group which had 2 levels (modafinil user vs. nonuser). There were various dependent variables of interest, including response inhibition (go/no-go: total errors, go errors, no-go errors, horizontal errors, vertical errors, total response rate, vertical response rate and horizontal response rate), sustained attention (continuous performance: hits, misses and response time) and working memory score (2-back: hits, misses, correct rejections, false alarms and no response).

6.3.3 Materials

Participants completed a total of 3 cognitive performance measures: the 2-back working memory task, a visual cued version of the Go/No-go task and the continuous performance task. They also filled in the Hospital Anxiety and Depression Scale (HADS) and a modified version of the Background Drug Use Questionnaire to investigate their substance use history. Each measure is fully described below:

6.3.3.1 Hospital Anxiety and Depression Scale (HADS)

The HADS is a clinical measure of state anxiety and depression (Zigmond & Snaith, 1983). Seven items assess anxiety and 7 assess depression. Questions are presented as statements on a 4-point Likert scale (e.g., 0 = Not at all, 3 = Most of the time) such as; 'I feel tense or 'would up' (anxiety) and 'I can laugh and see the funny side of things' (depression). Anxiety and depression score are tallied separately and reported at the bottom of the paper (0 – 7

= Normal, 8 – 10 = Borderline abnormal, 11 – 21 = Abnormal). Reliability analysis with data from this study revealed strong internal consistency for anxiety (α = .812) and depression scores (α = .898).

6.3.3.2 Modified Background Drug Use Questionnaire

The modified Background Drug Use Questionnaire is a measure of substance use patterns derived from the Background Drug Use Questionnaire (see Montgomery et al., 2005 for original survey). This version emphasises modafinil use but also investigates an inventory of other drugs and other background variables.

i) Substance Use.

At the onset of the survey participants are asked if they have ever used modafinil (yes/no) and if so for how long (months/years). Use of a comprehensive list of other psychoactive drugs is then assessed, including: alcohol, amphetamine, cannabis, cocaine, crack, DMT, GHB, herbal E, heroin, ketamine, LSD, LCB, mushrooms, poppers, Prozac, salvia divindrum, tranquillisers, tobacco, Viagra, steroids, mephedrone and naphyrone. Past use is explored including when respondents first began using (month and year) and when they last used (hours, days, weeks, months or years previous). Frequency of use in the previous 12 months is also investigated (e.g., tablets/grams/mg taken in one session and over the course of a week/month/year).

ii) Other Variables.

Respondents are asked about their: age, gender, qualifications (CSE, GCE, GCSE, A-level, NVG, Government employment training scheme, craft/trade, HND, degree, 'other' and none), previous convictions (drug related or not), living circumstances (live alone, with parents, with partner, marriage partner, single parent family, live with friends, no fixed

abode or 'other') their current employment status (full-time, part-time, unemployed, self-employed, student or 'other'). and units of alcohol normally consumed (daily, weekly, fortnightly, monthly or 'other'). They are also asked general health related questions for participant screening, including; whether they have been hospitalised with a specific condition (neurological, heart or respiratory) whether they have a diagnosis of a clinical disorder (diabetes, anxiety, depression, flashbacks, panic attacks, paranoia, phobias or schizophrenia), and whether they consider themselves in good health (very good, good, average, poor or very poor) .

6.3.3.3 *2*-Back Working Memory Task

The *n*-back task presents participants with a sequence of letters/numbers that appear one at a time on a computer screen (Owen, McMillan, Laird, & Bullmore, 2005). Depending on the difficulty of the condition used, participants have to identify whether the letter currently presented on screen matches a letter presented 'X' number of items previously. The higher the value of *n*, the greater the working memory demand. This study used a *2*-back paradigm, requiring participants to identify letter matches two stimuli apart. In both conditions, black letters appeared one at a time in bold Times New Roman font overlaid against a white screen. Items were presented for 1500 ms and responses were recorded in a further 500 ms window following the presentation of the letter. For the *2*-back, the task was presented in a single block with a total duration of 5 minutes. Participants were required to press '5' on the number pad when they recognised a hit, and '1' for non-hit. In both conditions, participants completed a short practice trial before the experiment and received a percentage of accuracy based on total hits. At the conclusion of the test participants received a breakdown of their total hits, misses, correct rejections and no

responses. This version of the *2*-back was created using E-Prime software by Psychology Software Tools (Kirchner, 1958).

6.3.3.4 Cued Go/No-Go Task

A test of response inhibition, participants are exposed to a transparent rectangle that appears in the centre of a white computer screen in either a vertical or horizontal configuration (Nosek & Banaji, 2001). After a small delay, the rectangle is changed to either blue or green and presented for 500 ms. Participants are instructed to press the space bar as fast as possible on a keyboard provided if the rectangle turns green, but not if it turns blue. Responses are recorded within the 500 ms timeframe. The task is presented in three blocks and has a total duration of ten minutes. This version of the Go/No-Go Task was downloaded and run using Inquisit.

6.3.3.5 Continuous Performance Task

A task assessing prolonged attention which has previously been used to investigate the cognitive effects of stimulant medications (Riccio, Waldrop, Reynolds, Lowe, & neurosciences, 2001; Verbaten et al., 1994). Participants are presented with a random sequence of numbers which appear on a computer screen one at a time and range from 0 – 9. They are instructed to identify even numbers and press the space bar when they are encountered, but they must ignore odd numbers (zero is considered non-even). The task is presented in a single block of 10 minutes, and scores are stored as a text file after completion. This task was also downloaded and run using Inquisit.

6.3.4 Procedure

The current study was approved by Liverpool John Moores University Research Ethics Committee in October 2016. Participants were contacted and recruited from the local student cohort through mailing lists and a student research participation scheme, and via advertisements on speciality PCE user forums. In all emails and advertisements, recipients were provided with a digital copy of the PIS which outlined the study aims and exclusion criteria and what would be expected of them at the lab. Potential participants were excluded if they had a recent history of cardiac or clinical psychiatric conditions. On arrival, participants were also provided with a paper copy of the PIS and a consent form. After giving consent, they completed the modified Background Drug Use Questionnaire to provide information on modafinil use, other drug use patterns and demographic information, and they completed the Hospital Anxiety and Depression Scale. Following this, participants sat at a computer and completed the 3 computerised tasks. Order of task presentation was randomised. Participants completed: the *2*-back working memory task, the continuous performance task and the go/no-go task, each of which lasted approximately 10 minutes. After completing the tasks, participants received a paper debrief which explained the aims of the research and were provided with contact details for counselling and drug use information services.

6.3.5 Data Analysis Strategy

Data analysis was carried out using SPSS version 25, and ANOVA was used to analyse between-groups differences on all behavioural measures. Descriptive analysis was conducted on health screening questions to identify those participants who were ineligible to continue with the study although none were reported (i.e., had a neurological condition

or history of a clinical disorder). On the continuous performance task, data was first extrapolated using E-Data Aid from E-Prime software, and average hits, misses and response times were calculated and then transferred into an SPSS datasheet and analysed using univariate ANOVA. Additionally, where repeated ANOVA were run on the same data set (i.e., on a single cognitive performance measure), Bonferroni adjustments were made to alpha levels to minimise the occurrence of type-1 errors. Furthermore, to assess other factors which might influence performance on the tasks (i.e., use of other substances) hierarchical multiple regression was used. Regression analysis was conducted across 2 stages. In total, 6 regression models were carried out which assessed: 2-back hits, 2-back misses, Go/No-go total response rate, CPT hits, CPT misses and CPT response rate as dependent variables. Certain variables were excluded from analysis due to near indistinguishable performance between participants, such as hits and misses on the Go/No-go task. Additionally, average monthly modafinil use, total number of substances used in the previous 3 months, use of illegal stimulants, (i.e., cocaine and amphetamine use), cannabis and alcohol in the previous year were predictor variables. At stage 1 of the regression, average monthly modafinil use was the only predictor, and at stage 2 drug use variables found to at least approach significance with behavioural variables in bivariate correlations were included. This order was chosen because investigating long-term modafinil use is central to the aims of this study, and because, as previously discussed, the drug is shown to affect cognitive processes which are implicated in the cognitive tasks. A correlation matrix was also created between predictor variables to assess collinear relationships and investigate patterns of polydrug use in the sample.

6.4 Results

6.4.1 Demographics

Analysis of drug use demographics revealed recent use of multiple substances throughout the sample. For instance, the modafinil user group reported a mean average use of 5.74 (SD = 4.43) tablets a month over the past year, with average tablet intake ranging from 2 to 16 in the sample. Moreover, in the previous 3 months participants reported use of multiple substances listed in the modified Background Drug use Questionnaire (mean = 3.03, SD = 2.49). However, when prevalence was investigated between the user groups, a t-test revealed that the modafinil group used significantly more substances than nonusers ($t(33) = 4.160$, $p < .05$, $d = .32$) (users: Mean = 4.67, SD = 2.84; nonusers: Mean = 1.47, SD = 1.04). Alcohol, illegal stimulant and cannabis use was also assessed, but due to low response rates across the sample on these measures, frequency of use could not be investigated and instead analysis focused on whether or not these substances had been used in the past year. For alcohol, 74% reported use and there were no apparent differences between user groups ($t(33) = .303$, $p > .05$, $d = .00$). With illegal stimulants, use was markedly lower at 44%, and again there were no statistically significant differences between groups ($t(33) = 1.677$, $p > .05$, $d = .11$). Finally, cannabis use was higher than stimulant use, with 55% reported prevalence, but like the other substances, groups did not significantly differ in use ($t(33) = .809$, $p > .05$, $d = .10$).

Furthermore, 79% ($N = 27$) of the sample recorded some degree of educational attainment. All respondents indicated that they had achieved level 2 (GCSE or equivalent) and level 3 (A-level, NVQ or equivalent) qualifications prior, which was unsurprising as many were students currently study at university. Additionally, all participants reported that they were in the process of completing a higher education qualification (degree/diploma equivalent or higher), but few stated having level 6 qualifications or higher (users: $N = 1$; nonusers: $N =$

3). Consequently, meaningful analysis between groups could not be conducted as they appeared to be matched.

6.4.2 Behavioural Measures

Anxiety and depression score on the HADS are recorded in Table 6.1. Univariate ANOVA found no significant between-groups differences in self-reported anxiety or depression between modafinil users and nonusers.

Table 6.1 – Average modafinil user and nonuser scores on the HADS.

HADS	Long-term Modafinil Users	Nonusers	ANOVA
	Mean (SD)	**Mean (SD)**	***F*(1,33)** **Sig**
Anxiety	**5.67 (3.39)**	**5.29 (3.73)**	.074, p >.05, η_p^2 = .003
Depression	**3.83 (2.98)**	**2.93 (2.92)**	.443, p >.05, η_p^2 = .025

Results from the *2*-back are displayed in Table 6.2. Despite users on average appearing to have marginally more hits and fewer misses than nonusers, findings from univariate ANOVA were not statistically significant. Furthermore, the groups did not significantly differ on total correct rejections, false alarms or in failed responses, suggesting that working memory performance overall was not impacted by modafinil user status.

Table 6.2 – Performance on the 2-back working memory task between modafinil users and nonusers.

2-back	Long-term Modafinil Users	Nonusers	ANOVA		
	Mean (SD)		***F*(1,33)**	**Sig**	**Effect**
Hits	**22.87 (4.67)**	**20.16 (6.65)**	1.786	>.05	η_p^2 = .051
Misses	**5.33 (4.35)**	**7.26 (4.25)**	.203	>.05	η_p^2 = .050

Correct Rejections	**50.87 (15.65)**	**47.58 (16.78)**	.563	>.05	η_p^2 = .011
False Alarms	**1.40 (2.37)**	**1.84 (3.28)**	1.039	>.05	η_p^2 = .031
No Response	**9.53 (20.14)**	**12.21 (22.51)**	.130	>.05	η_p^2 = .004

Performance scores on the Go/No-go task are displayed in Table 6.3. Regardless of user group, errors were minimal. Moreover, univariate ANOVA revealed no between-groups differences in total errors, 'go' target errors and 'no-go' target errors. Interestingly, ANOVA revealed a significant difference in response time between user groups, and inspection of descriptive statistics revealed that modafinil users had quicker response times overall, and when cues were presented both vertically and horizontally. This finding suggests that while user status might not impact response, it may influence attentional speed without a trade-off in accuracy.

Table 6.3 – Performance scores for total errors and response rates in milliseconds to the different stimuli on the Go/No-go task.

Go/No-go	**Long-term Modafinil Users**	**Nonusers**	**ANOVA**		
	Mean (SD)		***F***(1,33)	**Sig**	**Effect**
Total Errors	**.004 (.006)**	**.003 (.004)**	.135	>.05	η_p^2 = .004
Go Target Errors	**.001 (.003)**	**.000 (.000)**	1.740	>.05	η_p^2 = .052
No-go Target Errors	**.007 (.011)**	**.006 (.006)**	.042	>.05	η_p^2 = .001
Response Rate Total	**322 (37.40)**	**357 (48.71)**	*5.130	<.05	η_p^2 = .158

*Significant at .05

Results from the CPT are displayed in Table 6.5. Although users appeared to have marginally more hits than nonusers, univariate ANOVA revealed that there were no

significant between-groups differences in total hits or misses. Moreover, the response time advantage seen in the Go/No-go task was not evident in the CPT.

Table 6.4 – Performance scores for total hits, misses and response rate in milliseconds to number pairs on the CPT.

CPT	Long-term Modafinil Users	Nonusers	ANOVA		
	Mean (SD)		*F*(1,33)	Sig	Effect
Hits	**759.27 (37.33)**	**725.63 (177.48)**	.517	>.05	$\eta_p^2 = .016$
Misses	**80.73 (37.33)**	**70.16 (30.19)**	.835	>.05	$\eta_p^2 = .025$
Response Rate	**456.52 (37.99)**	**442.07 (111.87)**	.228	>.05	$\eta_p^2 = .007$

Response time recorded in milliseconds.

6.4.3 Hierarchical Regression

Standardised beta coefficients, and significance values for substance use variables and their impact on task performance are presented in Table 6.6. Prior to carrying out multiple regression analysis, the required assumptions were tested and met. To examine multicollinearity, a Pearson's *r* correlation matix was run and is presented in Table 6.5. Furthermore, analysis was conducted in 2 stages, first assessing the impact of average monthly modafinil use over the past year, then by including the use of other substances in a second model. The second stage of the model was determined by examining bivariate correlations between substance use variables and the respective task performance variables. This was done instead of entering all variables into the model because the sample size lacked the appropriate statistical power for a more ambitious design. As such, those substance use variables which approached significance were included in stage 2. In total, 6 analyses were conducted, revealing mixed fingings.

Table 6.5 –Pearson's r coefficients for drug use variables derived from self-reported use on the Background Drug Use Questionnaire.

Pearson's *r* Correlations	***Total No. of Substances Used: 3 months***	***Total Stimulant Use: Previous year***	***Total Cannabis Use: Previous year***	***Total Alcohol Use: Previous year***
Average Monthly Modafinil Use	***.322**	.253	.329	.096
Total No. of Substances Used: 3 months		***.375**	.302	.165
Total Stimulant Use: Previous year			***.382**	.184
Total Cannabis Use: Previous year				***.378**
Total Alcohol Use: Previous year				

N:34 (15 modafinil users). *Significant at .05

Pearson's correlational analysis found several moderate significant relationships between drug use variables. Predictably, total number of substances used in the previous 3 months was significantly correlated with the number of participants who reported illegal stimulant use in the last year (r = .375, p < .05). Moreover, stimulant use was also moderately correlated with cannabis use (r = .382, p < .05), and cannabis use was in turn correlated with previous year alcohol use (r = .378, p < .05). This implies that people who used one illegal drug were more likely to use another, suggesting that polydrug use was prevalent in the sample. Nonetheless, average monthly modafinil use over the past year was not significantly correlated with any other substance use variable, suggesting that modafinil users tended not to have recent experiences of polydrug use. Furthermore, despite some

moderate correlations, coefficients were of acceptable collinearity (Field, 2013), meaning that multiple regression could be conducted

When drug use variables were correlated against the respective behavioural measures, findings were mixed. As the study was primarily concerned with investigating modafinil use, average monthly modafinil use was included based on theoretical assumptions rather than assessing the strength of bivariate correlations first. Nevertheless, for total number of substances used in the previous 3 months, Go/No-go response rate was moderately significantly correlated (r = -.314, p < .05), and CPT misses approached significance (r = .251, p = .07). Previous year stimulant use was significantly negatively associated with CPT hits (r = -.296, p < .05) but no other variable, and previous year cannabis use was only negatively associated with CPT response rate (r = -.335, p < .05). Finally, previous year alcohol use was moderately negatively correlated with *2*-back hits (r = -.301, p < .05) and highly positively correlated with *2*-back misses (r = .479, p < .01). All other associations between drug use and behavioural variables were non-significant and thus not included in the second stages of the regression analyses

Table 6.6 – Standardised Beta coefficients for substance use variables and performance on different aspects of the behavioural measures. Substance use variables were subject to bivariate correlation analysis prior to performing multiple regression to predict model strength and to screen for which factors were unsuitable in the analyses.

Hierarchical Regression	*2*-back: Hits	*2*-back: Misses	G/NG R. Rate: Total	CPT: Hits	CPT: Misses	CPT: R. Rate
Stage 1	**Standardised Beta Coefficients**					
Average Monthly Modafinil Use	.258	-.160	***-.423**	.066	.208	-.013
Stage 2						
Average Monthly Modafinil Use	.284	-.204	****-.450**	.137	.191	.088
Total No. of Substances Used: 3 months	-	-	.084	-	.055	-
Total Stimulant Use: Previous year	-	-	-	-.282	-	-
Total Cannabis Use: Previous year	-	-	-	-	-	-.308
Total Alcohol Use: Previous year	-.275	***.459**	-	-	-	-

N: 33 (15 modafinil users). t-test df = 32. *Significant at .05. **Significant at .01. Abbreviation: G/NG, Go/No-go. R. Rate, Response Rate.

Hierarchical regression revealed that *2*-back hits was not predicted at stage 1 ($F(1,32) = .005$, $p > .05$; *F* change: $F(1,32) = 2.275$, $p > .05$) or 2 ($F(1,32) = 1.436$, $p > .05$) of the analysis. For *2*-back misses, findings diverged, as stage 1 was non-significant ($F(1,32) = .842$, $p > .05$; *F* change: $F(1,32) = .336$, $p < .05$) but stage 2 was successful ($F(1,32) = 4.746$, $p < .05$). At stage one, R^2 only explained 2.6% of variation in misses, but at stage 2 this increased to 23.4%. This is no doubt because use of alcohol in the previous year was a significant predictive factor, with alcohol users demonstrating more misses than nonusers. On Go/no-go total response rate, stage 1 ($F(1,33) = 6.976$, $p < .05$; *F* change: $F(1,32) = 6.976$, $p < .05$) of analysis was statistically significant, and so was stage 2 ($F(1,33) = 3.527$, $p < .05$). At stage 1, R^2 explained 17.9% of variance in response rate, which rose to 20.1% at stage 2. However, only average monthly modafinil use was a notable predictor at both stages of analysis, proving significant at stage 1 and highly significant at stage 2. As such, findings indicate that increased frequency of modafinil use alone predicted faster response times on the Go/No-Go task. Finally, regression showed null findings on the CPT, as the model was non-significant at accounting for variance in hits at stage 1 ($F(1,33) = .138$, $p > .05$; *F* change: $F(1,32) = .138$, $p > .05$) and 2 ($F(1,33) = 1.325$, $p > .05$), misses at stage 1 ($F(1,33) = 1.452$, $p > .05$; *F* change: $F(1,32) = 1.452$, $p > .05$) and 2 ($F(5,33) = .749$, $p > .05$) and response time at stage 1 ($F(1,33) = .005$, $p > .05$; *F* change: $F(1,32) = .005$, $p > .05$) and 2 ($F(5,33) = 1.436$, $p > .05$). As such, recent use of modafinil and other substances did not appear to predict variability in prolonged attention on the CPT.

6.5 Discussion

The findings from this study did not support most hypotheses outlined earlier in the Chapter. In fact, in some incidences, results suggest the opposite of what was predicted.

For instance, examination of studies with illegal stimulants suggested that, given the similar mechanism of action in the dopamine system with modafinil, users would exhibit deficits in cognitive performance, which would be expressed by poorer performance on the cognitive tasks. This was not found to be the case. In fact, modafinil users demonstrated decreased response time compared with controls on the Cued Go/No-go task and a similiar amount of hits and misses, inferring that they had increased attentional speed without a trade-off to accuracy. Furthermore, greater frequency of modafinil use did not predict performance on the cognitive measures. However, more frequent use was a significant predictor of a quicker response rate on the Go/No-go, and taken together with total number of substance used in the previous 3 months, both stages of the model significantly predicted response time. Together with greater alcohol use in the previous year, reduced frequency of modafinl use also predicted *2*-back misses but not hits. For CPT hits, misses and response rate, all substance use variables were non-significant. Finally, there was a significant moderate positive correlation between modafinil use and polydrug use over the previous 3 months. Therefore, as modafinil users showed no behavioural differences in some tasks and improved performance in attentional speed, the H^5 and H^6 could not be accepted. However, modafinil users did use more substances than nonusers, and as such the H^7 was accepted.

Despite research with illegal stimulants showing cognitive deficits in long-term stimulant users, the current study revealed that modafinil users perform better in some measures of cognitive performance. This suggests that, contrary to expectations and despite the neurochemical similarities with illegal stimulants, that long-term modafinil use may not lead to the same deficits. In fact, findings show similarity to Müller and colleagues' acute administration research which demonstrated increased attentional speed without an accuracy trade-off, and research by Marchant et al. (2009) which showed a general

increase in speed of attention. Of course, in the current study, users had been abstinent from modafinil for at least 48 hours, a period of time shown earlier in this Chapter to fully deplete the psychoactive effect of the drug, suggesting that benefits conferred from this substance may continue to exist after the acute effects have expired. Given that there were no improvements in the CPT or *2*-back hits, it is possible that either this is an artefact in the data, or that attentional speed may only be improved under specific circumstances. It is also possible that the lack of pronounced differences in working memory performance may be attributable to the fact that the *2*-back was too easy, and an increase in difficulty may demonstrate behavioural differences between user groups. However, in spite of this apparent limitation, no other study has yet demonstrated benefits to cognitive performance in long-term modafinil users. As such, future research should aim to further investigate modafinil use and cognition, and focus on harder working memory paradigms and tasks that assess response inhibition.

6.6 Chapter Summary

This chapter explored cognitive performance on various behavioural measures in long-term modafinil users vs. nonusing controls. Findings indicated that, while users showed no advantages over nonusers on working memory performance or sustained attention, they did perform significantly faster on a response inhibition task without sacrificing accuracy, which is consistent with previous acute administration studies. As a result, findings did not support most hypotheses previously outlined, suggesting that although modafinil may have a similar mechanism of action to illict stimulants like cocaine, the drug's effects on the brain and cognition appear such that it might improve performance in certain cognitive domains even after acute psychoactive effects have expired. As such, the results appear to contradict expectations, implying that modafinil acts in a unique capacity on the brain to

illegal stimulants. In order to further explore these unexpected findings, the final study of this thesis uses the neuroimaging technology fNIRS to explore prefrontal brain activation in modafinil users when they complete cognitive performance measures which induce greater cognitive workload, including a harder *3*-back working memory test and different difficulty conditions of the MTF. Moreover, measures of HRV and blood pressure are also included to make a wider assessment of long-term modafinil use on cardiovascular functioning, to see whether the drug also has a physiological impact.

Chapter 7: Study 3 – Long-Term Modafinil use, Psychophysiological and Neurophysiological Indicators of Effort: Findings from functional near-infrared spectroscopy and electrocardiogram.

7.1 Chapter Overview

In the previous chapter, cognitive performance was assessed across several cognitive performance measures, comparing modafinil users and nonusers. However, various findings which defied expectations led to the need for further inquiry. This chapter describes a study which examines the neurophysiological correlates of cognitive effort, using fNIRS, ECG and blood pressure measurements to investigate haemodynamic response and autonomic activity between user groups during completion of a more challenging *3*-back working memory task and a multitasking paradigm.

7.2 Introduction

Cognitive deficits from chronic illegal stimulant use are well documented (Gouzoulis-Mayfrank & Daumann, 2009). These deficits are thought to stem from dopaminergic deregulation and destruction of dopamine transporters, with long-term use shown to lead to adverse psychological and physical health outcomes (McCann & Ricaurte, 2004; Pereira, Andrade, & Valentão, 2015). Moreover, studies have highlighted persistent deficits in working memory and executive function in chronic stimulant users (Reske, Eidt, Delis, & Paulus, 2010; Vonmoos et al., 2014), as well as higher than average blood pressure and irregular HRV (Koenig, Menke, Hillecke, Thayer, & Jarczok, 2015). However, despite some similarities in method of action with illegal stimulants, little is known about the long-term impact of PCEs on cognitive, neurological and cardiovascular functioning.

Neuroimaging technologies are robust instruments for capturing neuronal activity, and a wealth of research has already shown that they can provide neurological correlates of cognitive deficits (Ranchet et al., 2017; Unni et al., 2015). Additionally, the emergence of fNIRS has provided a means of observing haemodynamic response to neuronal activation, which studies reveal is sensitive when localising cognitive impairments in working memory and executive function (Ehlis et al., 2008; Izzetoglu et al., 2004). The DLPFC is particularly accessible with fNIRS, which several recent studies have illustrated with ecstasy polydrug users. For instance, in one study, increased activation in the left DLPFC but a lack of behavioural differences on the Chicago World Fluency Test showed that ecstasy users experienced increased cognitive workload relative to controls, suggesting underlying cognitive deficits (Roberts & Montgomery, 2015a). Furthermore, on a letter generation inhibitory control task, the same authors found that ecstasy users experienced increased oxy-Hb change in the left and right DLPFC again with no differences in behavioural output (Roberts & Montgomery, 2015b). Additionally, with working memory performance, ecstasy users demonstrate increased activation in the left and right DLPFC without performance differences on a verbal and spatial updating task, with recent use and greater levels of use both linked to working memory deficits (Montgomery et al., 2017). Still, a study by the same group showed that on the MTF, ecstasy users exhibited decreased oxy-Hb change relative to nonusers despite similar performance on all subtasks, suggesting that while some cognitive domains may be negatively impacted by use, others may improve (Roberts et al., 2015). Research using fNIRS in prescription stimulant users is extremely limited and focuses on adolescent with ADHD. For example, it has been demonstrated that adolescents prescribed MPH show greater right DLPFC activation relative to controls without behavioural differences in response inhibition (Moser et al., 2009). Furthermore, on an *n*-back task, adolescents with ADHD showed reduced oxy-Hb change compared with controls in the VLPFC and a significantly worse working memory performance, suggesting that

cognitive deficits may also be linked to reductions in VLPFC activity (Ehlis et al., 2008). Finally, on a go/no-go task, ADHD adolescents exhibited increased right PFC activation and better task performance after MPH administration than before it, implying that greater activity in the region is associated with improved response inhibition (Monden et al., 2012). Therefore, fNIRS appears to be a suitable tool for capturing the neurological link between cognitive deficits and increases in cognitive workload.

Studies with the cardiovascular system have also assessed stimulant use. For instance, long-term use of cocaine and amphetamine is associated with cardiovascular toxicity and in extreme cases can lead to myocardial infarction and even death (Richards et al., 2016). Such drugs stimulate the SNS via various neurotransmitter networks, which in turn increases oxygen demand on the heart and heightens blood pressure (Stankowski et al., 2015). However, there is little research assessing adult stimulant use and the impact on HRV. A recent systematic review found that in studies with adult users of cocaine, high-frequency HRV was reduced in resting state (Koenig et al., 2015), although no studies have been identified which investigate the effects of long-term PCE use on HRV, despite recent evidence that shows acute use of both MPH and modafinil increase heart rate and SBP (Li et al., 2017; Taneja et al., 2005).

As such, despite some compelling findings using neurophysiological methods to investigate substance use during completion of cognitive performance measures, studies have failed to investigate long-term nonmedical modafinil use, despite the pharmacological similarities shared with illegal stimulants. The current research aims to assess changes in prefrontal haemodynamic response, blood pressure and HRV in response to a working memory and a multitasking stressor in modafinil users and non-using controls. Following on from the previous study which focused solely on behavioural performance, oxy-Hb change, high frequency HRV and systolic and diastolic blood pressure are also recorded to address

psychophysiological and neurophysiological indicators of effort and to address several hypotheses. It was anticipated that long-term modafinil users would exhibit differences in haemodynamic response which would occur bilaterally in the left and right DLPFC indicating increased cognitive effort when compared with controls during the cognitive performance measures (H^{8}). Differences were also expected to be observed in heart rate variability and blood pressure, with users anticipated to show atypical heart rate variability and elevated blood pressure (H^{9}). All participants would exhibit increased haemodynamic activity and blood pressure as well as a significant reduction in R-R interval relative to baseline during the cognitive tasks. This was expected to be more pronounced in the hard condition than the easy condition (H^{10})**.** Long-term modafinil users would report a significantly greater mental effort on the NASA-TLX than nonusers, and this would escalate with increasing task difficulty. Furthermore, they would also perform significantly worse on the cognitive performance measures (H^{11}).

7.3 Method

7.3.1 Participants

Data was collected from February 2018 to December 2018. Thirteen modafinil users (mean age = 24.72, SD = 4.37, males = 100%) and 21 non-using controls (mean age = 26.62, SD = 3.65, males = 62%) were recruited with an opportunity sampling and snowball sampling method via university mailing lists and online CE user forums. However, as the modafinil user sample was entirely male, females were excluded from the control group so that the groups were gender-matched, bringing the final number for analysis to 13 modafinil users and 10 nonusers (mean age = 26.25, SD = 2.43). To be considered a modafinil user, participants had to have used modafinil for a minimum of 12 months and at least once a

month, and nonusers had to have no history of modafinil use, although a history with use of other substances was permitted. Furthermore, participants were only eligible if they abstained from psychoactive substances other than caffeine for 48 hours before the study.

7.3.2 Design

A mixed design was used to analyse neurophysiological and behavioural data. The between-groups variable was user group which had 2 levels (modafinil users vs. nonusers). There were several within-groups factors across all measures. On the MTF difficulty conditions (low and high), within-group comparisons were made across each subtask and score totals. Differences in perceived workload recorded on the NASA-TLX were also analysed between MTF difficulty conditions and the *3*-back. For neurophysiological data, differences in oxy-Hb change, blood pressure and HRV were made between the tasks. There were several dependent variables of interest, including: task scores, haemodynamic response, HRV and blood pressure.

7.3.3 Materials

Participants completed the *3*-back and low and high difficulty variants of the MTF while fastened into the fNIRS cap and wearing ECG electrodes and a blood pressure monitor (All neurophysiological apparatus is fully described in Chapter 4). All questionnaire and cognitive performance measures are detailed below:

7.3.3.1 Hospital Anxiety and Depression Scale (HADS)

The HADS is a clinical measure of state anxiety and depression and is fully described in Chapter 6 (Zigmond & Snaith, 1983). Reliability analysis with data from this study

demonstrated good internal consistency for anxiety (α = .755) and depression scores (α = .796).

7.3.3.2 Modified Background Drug Use Questionnaire

The modified Background Drug Use Questionnaire is a measure of substance use patterns derived from the Background Drug Use Questionnaire which emphasises modafinil use (see Montgomery et al., 2005 for original survey). This version is fully described in Chapter 6.

7.3.3.3 NASA Task Load Index (NASA-TLX)

The NASA-TLX is a measure of subjective workload completed at the conclusion of a task (Hart & Staveland, 1988). There are 6 subscales (mental demand, physical demand, temporal demand, personal performance estimation, total effort and frustration) each presented on a 100mm visual analogue scale. Participants are required to mark somewhere across each line in pencil to indicate their perceived workload. Responses toward the right side indicate high workload, and those toward the left suggest low. Subscales are calculated using a ruler and scores can be obtained for each individual type of workload or averaged together into a singular measure of perceived workload.

7.3.3.4 *3*-Back

The *n*-back task presents participants with a sequence of letters/numbers that appear one at a time on a computer screen (Owen et al., 2005). Depending on the difficulty of the condition used, participants have to identify whether the letter currently presented on screen matches a letter presented 'X' number of items previously. The higher the value of

n, the greater the working memory demand. This study used a *3*-back paradigm, requiring participants to identify letter matches 3 stimuli apart. In both conditions, black letters appeared one at a time in bold Times New Roman font overlaid against a white screen. Items were presented for 1500 ms and responses were recorded in a further 500 ms window following the presentation of the letter. For the *3*-back, the task was presented in 3 blocks for a total duration of 10 minutes. Participants were required to press '5' on the number pad when they recognised a hit, and '1' for non-hit. In both conditions, participants completed a short practice trial before the experiment and received a percentage of accuracy based on total hits. At the conclusion of the test participants received a breakdown of their total hits, misses, correct rejections and no responses. This version of the *3*-back was created using E-Prime software by Psychology Software Tools (Kirchner, 1958).

7.3.3.5 The Multitasking Framework

The Multitasking Framework (created by Purple Research Solutions UK) is a paradigm for assessing cognitive demand using a montage of performance-driven tasks that can be completed alone or simultaneously to examine different aspects of executive function (Wetherell, Sidgreaves, & Stress, 2005). The more tasks participants are required to complete, the greater the cognitive load. Difficulty can also be manipulated by altering the speed or workload of the different tasks. There is a total of eight tasks which can be selected, each examining different cognitive functions. Participants can complete up to four tasks at once which appear in an onscreen window divided into quadrants. A numerical score is presented at the centre of the window which increases in value as participants succeed in the tasks but decreases if they respond incorrectly or fail to adequately split their attention between quadrants. This test has previously been used in similar studies

which measure stress and cognitive demand in long-term substance users (Parrott et al., 2014; Roberts et al., 2015; Wetherell, Atherton, Grainger, Brosnan, Scholey, et al., 2012). In this study, this framework was divided into two difficulty conditions: low and high. In both conditions, participants were exposed to four tasks: visual monitoring, psychomotor, mental arithmetic and a Stroop test.

Visual monitoring task. A task examining attention monitoring, participants encounter a dot in the centre of a series of concentric circles which steadily moves toward the outer ring. A higher score is awarded if the dot is reset when it is closer to the outermost circle. However, if the dot passes the final circle then a score penalty is applied for each second that it is not reset.

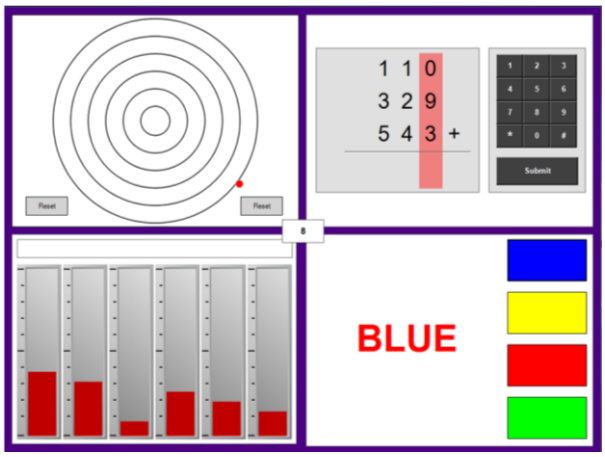
Visual warning task. A test examining psychomotor functions, six stunted red bars appear alongside each other and build to different heights continuously throughout the test. Once the bars have reached maximum height a flashing red warming message appears. Each bar is assigned a number from 1 – 6 with the tallest being assigned 6 and the smallest 1. Participants are required to select each bar from tallest to smallest and turn the display from red to green so that the bars can reset and be reduced to equal size. If the bars are reset immediately after the warning then points are awarded, but if they are selected in the wrong order or after a delay then a penalty is incurred.

Mental arithmetic. A test of working memory, participants complete a series of sums consisting of two or three digits depending on difficulty, and are required to add, subtract or divide. Correct answers award points, but incorrect answers or response delays incur a penalty.

Stroop test. A test of inhibitory control, participants are exposed to the following group of four colour names which appear one at a time on the screen: ‘Red’, ‘Blue’, ‘Yellow’ and ‘Green’. However, each name is presented in a different colour font to what the name

suggests (i.e., 'Blue' is presented in red font), and participants are required to identify the colour of the word and not what it reads. Four colour pallets are presented alongside the word and participants must select the right colour. The right selection awards points, but incorrect inputs incur penalties.

Figure 7.1 – The Multitasking Framework in progress. Tasks are divided into 4 quadrants and a numeral score is displayed at the centre of the window.



7.3.4 Procedure

This study was approved by Liverpool John Moores University Research Ethics Committee in December 2017. Participants were recruited from the university and the surrounding area through LJMU email lists and online PCE discussion groups. A digital copy of the participant information sheet was provided in all correspondences which detailed the aims of the study and what would happen to participants in the lab. On arrival, participants also received a paper copy of the PIS and a consent form. After giving consent, participants completed the Modified Background Drug Use Questionnaire, to collect demographic information and assess modafinil and other substance use history, and the Hospital Anxiety and Depression Scale. Functional near-infrared spectroscopy and ECG electrodes were then fastened to the participant and their left arm was placed in a blood pressure cuff. A 3-

minute montage of relaxing images and music was then played on a computer while baseline recordings from fNIRS, ECG and the blood pressure cuff were taken. Following baseline measures, participants were randomly allocated to complete either the easy or hard condition of the Multitasking framework (MTF) which lasted approximately 10 minutes. After a short break, they were administered the *3*-back which lasted another 10 minutes. Finally, participants completed the remaining difficulty condition of the MTF and after completion were provided with a paper debrief. During all cognitive tasks, recordings from fNIRS, ECG and blood pressure were taken, and at the conclusion of each task participants filled out the NASA-TLX to assess perceived workload.

7.3.5 Data analysis strategy

Neurophysiological data was cleaned using various software packages. For fNIRS, the OxyMon integrated software Oxysoft by Artinis Medical Systems was used to clean signal noise and remove movement artefacts. This was achieved by applying low and high pass filtering to eradicate interference caused by ambient light sources and the cardiovascular system, and by eyeballing the data graph for sharp spikes (movement artefacts) and manually removing them. Raw data was also subject to CBSI analysis, which removes positive correlations between oxy and deoxy-Hb, thus improving signal quality and only requiring analysis of oxy-Hb data (see Chapter 4 for full details). AcqKnowledge, the accompanying analysis package of BSL PRO, was used on ECG raw signal data. Data analysis was conducted with SPSS version 25. For the behavioural data, several mixed MANOVA compared user groups and general differences in performance between the MTF difficulty conditions and the subtasks as well as differences on the 6 subscales of the NASA-TLX. Moreover, between-groups one-way ANOVA compared user groups on *3*-back hits and misses. For neurophysiological data, a series of mixed MANOVAs compared user groups

across tasks on haemodynamic changes between the right, medial and left prefrontal cortices and also looked at regional differences on the left and right DLPFC. Partial correlations were also run on each fNIRS channel while controlling for the remaining channels to compare regional connectivity during the tasks between the groups. User groups were also compared on high frequency HRV and SBP and DBP scores, and general differences between tasks were also assessed.

7.4 Results

7.4.1 Educational Attainment

All participants indicated some kind of prior educational attainment (*N* = 23). As in the previous study, every respondent recorded a level 2 (GCSE or equivalent) and level 3 (A-level, NVQ or equivalent) qualification. Furthermore, most participants were currently enrolled in higher education (*N* = 21), except for two nonusers who failed to provide a response. Therefore, educational attainment appeared to be matched between user groups.

7.4.2 Behavioural Measures

Anxiety and depression scores on the HADS are presented in Table 7.1. Between-groups ANOVA found that there were no significant differences between user groups on anxiety or depression score (see Table 7.1).

Table 7.1 – Average modafinil user and nonuser scores on the HADS.

HADS	Long-term Modafinil Users	Nonusers	ANOVA		
	Mean (SD)	**Mean (SD)**	***F*(1,19)**	**Sig**	**Effect**
Anxiety	5.38 (3.59)	7.13 (6.01)	.699	p >.05	η_p^2 = .035
Depression	3.00 (2.27)	4.75 (4.95)	1.234	p >.05	η_p^2 = .022

Average performance on the MTF and 3-back are presented in Table 7.2 and Table 7.3. A mixed MANOVA analysing differences on the MTF difficulty conditions found a non-significant within-groups effect on overall score (F(1,21) = 1.868, p > .05, η_p^2 = .099) with participants unexpectedly exhibiting a similar performance on the MTF easy condition and the hard condition. There was also a non-significant between-groups effect of users vs. nonusers (F(1,21) = .072, p > 05, η_p^2 = .009), however a follow-up ANOVA revealed that users did significantly better on the MTF high difficulty condition than nonusers (F(1,21) = 3.570, p < .05, η_p^2 = .198). Moreover, MANOVA on the subtasks of the MTF revealed several mixed findings. There was a significant within-groups difference between the MTF difficulty conditions (F(1,21) = 28.629, p < .001, η_p^2 = .799) but a non-significant between-groups effect of user group (F(1,21) = 2,300, p > .05, η_p^2 = .088). Moreover, post hoc t-tests revealed that, on average, participants scored higher on the low difficulty mental arithmetic task than the high difficulty, but unexpectedly did better on the high difficulty versions of the visual warning and tracking tasks while there was no significant difference on the Stroop (see Table 7.2). Furthermore, there was a significant condition x group interaction (F(1,21) = 3.684, p < .05, η_p^2 = .130), suggesting that users differed in performance to nonusers on the MTF difficult conditions. Follow-up post hoc *t*-tests revealed that on the high difficulty Stroop test, modafinil users scored significantly higher

than nonusers ($t(20) = 2.723$, $p < .05$, $d = .11$), but did not score differently on any other subtask. Finally, a one-way ANOVA found that on the 3-back, there were no significant between-groups differences between long-term users and nonusers on total hits and misses.

Table 7.2 – Average scores on the low and high difficulty conditions of the MTF.

MTF	**Long-term Modafinil Users**		**Nonusers**		***t*-test**
	Mean (SD)				***t*(1,20) =**
	Low Difficulty	**High Difficulty**	**Low Difficulty**	**High Difficulty**	**Within-groups results**
MTF Score	2675.38 (1244.03)	2832.31 (1503.00)	2480.50 (1615.89)	1503 (1432.49)	*2.127, <.05, *d* = .18
Arithmetic	193.85 (199.10)	42.31 (169.56)	185.00 (221.68)	41.25 (65.77)	***4.211, <.001, *d* = .54
Stroop	2157.69 (1215.01)	2165.38 (986.26)	1966.25 (1519.99)	790.13 (1327.43)	1.509, >.05, *d* = .08
Tracking	102.31 (37.57)	300.77 (205.04)	93.00 (39.06)	308.00 (293.44)	***-4.105, <.001, *d* = .52
Warning	223.08 (25.29)	352.50 (53.65)	226.25 (10.60)	352.50 (53.65)	***-8.133, <.001, *d* = .77

Note:* Significant at .05, **significant at .01, ***significant at .001

Abbreviation: MTF, multitasking framework.

Table 7.3 – Mean scores on the 3-back task between modafinil users and nonusers.

3-back	Long-term Modafinil Users	Nonusers	ANOVA		
	Mean (SD)		*F*(1,21)	Sig	Effect
Hits	11.69 (4.42)	9.25 (6.86)	.995	>.05	η_p^2 = .023
Misses	29.23 (9.94)	27.88 (9.74)	.093	>.05	η_p^2 = .002

Results on the NASA-TLX are displayed in Table 7.4. Mixed MANOVA revealed a highly significant within-groups effect of task on self-reported workload ($F(2,21) = 17.925$, $p < .001$, $\eta_p^2 = .666$). Additionally, a significant condition x subscale interaction was apparent ($F(5,21) = 38.554$, $p < .05$, $\eta_p^2 = .975$) suggesting that task-load across individual scales differed in relation to cognitive task. Moreover, repeated measures ANOVA on each subscale supported this finding as each was highly significant (see Table 7.4), and contrasts revealed a linear increase in self-reported task-load with the MTF easy condition requiring the least demand, followed by the MTF hard condition and then the 3-back on all subscales of the NASA-TLX. However, MANOVA revealed that there were no significant between-group differences observed among user groups ($F(1,21) = .635$, $p > .05$, $\eta_p^2 = .032$) and no significant condition x user group interactions ($F(1,21) = 1.920$, $p > .05$, $\eta_p^2 = .176$), indicating that long-term users did not differ to controls in any of the cognitive tests on self-reported task-load.

Table 7.4 – Mean scores on the subscales of the NASA-TLX for the cognitive tasks. Bonferroni adjustments were also made to alpha levels for the within-group ANOVA.

NASA-TLX	Modafinil Users			Nonusers			ANOVA
	Mean (SD)						*F*(2,21) =
MTF Conditions	Low Difficulty	High Difficulty	3-Back	Low Difficulty	High Difficulty	3-Back	Within-groups results
Mental	48.46 (23.20)	72.77 (17.48)	73.38 (14.06)	51.63 (18.60)	79.00 (23.58)	83.63 (16.65)	**28.337, p<.01, η_p^2 = .795
Physical	12.31 (11.63)	31.23 (27.26)	19.69 (20.15)	19.75 (15.13)	43.00 (38.78)	25.50 (23.43)	*6.126, p<.05, η_p^2 = .404
Temporal	51.31 (22.34)	70.77 (20.19)	65.85 (25.73)	51.63 (23.60)	78.38 (21.51)	70.13 (25.73)	**12.114, p<.01, η_p^2 = .539
Effort	57.23 (15.80)	74.08 (16.33)	75.38 (14.32)	49.50 (20.07)	75.00 (26.81)	79.38 (9.30)	**22.059, p<.01, η_p^2 = .726
Performance	64.23 (18.82)	48.08 (20.34)	26.15 (19.94)	62.38 (32.96)	50.63 (30.11)	31.00 (33.43)	**22.094, p<.01, η_p^2 = 719
Frustration	47.23 (25.60)	62.15 (18.37)	58.15 (28.30)	33.50 (29.60)	61.38 (23.57)	76.25 (17.86)	**9.849, p<.01, η_p^2 = .635

Note: * Significant at .05, **significant at .01. Abbreviation: MTF, multitasking framework.

7.4.3 fNIRS Analysis

Averages for oxy-Hb change from baseline among modafinil users and nonusers for the MTF low and high difficulty are shown in Table 7.5, and averages on the 3-back are presented in Table 7.6. Optodes were divided into regions of the PFC based on their position on the forehead (see Table 7.5 and table 7.6 for further details). Furthermore, the right PFC, medial PFC and left PFC were tested in separate MANOVA. Before multivariate analysis, bivariate correlations were carried out with optodes comprising each ROI. Optodes 8, 10 and 12 correlated significant with other channels in their respective regions and across multiple conditions, thus they were excluded from MANOVA due to multicollinearity.

Table 7.5 – Mean average oxy-Hb change on the MTF easy and hard conditions across the 12 optodes. The right PFC (optodes 1, 2, 7 and 8), medial PFC (optodes 3, 4, 9 and 10) and left PFC (optodes 5, 6, 11 and 12) are presented in different blocks.

	Modafinil users		Nonusers		MANOVA
	MTF Easy	**MTF Hard**	**MTF Easy**	**MTF Hard**	**Results**
Mean (SD) Oxy-Hb					
Right PFC					
Op 1	.12 (5.25)	-.33 (3.35)	-.01 (7.38)	-1.85 (4.63)	Group: $F(1,21) = 1.443$, $p > .05$, $\eta_p^2 = .071$
Op 2	-.94 (3.62)	-.47 (2.78)	3.20 (9.14)	2.98 (8.84)	Condition: $F(1,21) = 1.923$, $p > .05$, $\eta_p^2 = .092$
Op 7	2.67 (7.33)	.85 (6.10)	3.27 (3.79)	3.88 (4.48)	Region: $F(3,21) = 1.931$, $p > .05$, $\eta_p^2 = .092$
Op 8	-.85 (4.08)	.26 (5.56)	.81 (10.68)	.71 (10.80)	Group x condition = $F(1,21) = .026$, $p > .05$, $\eta_p^2 = .001$
Medial PFC					
Op 3	-1.89 (5.26)	-.29 (2.51)	-3.10 (6.04)	-1.55 (6.39)	Group: $F(1,21) = 2.555$, $p > .05$, $\eta_p^2 = .142$
Op 4	1.67 (3.25)	2.63 (7.51)	-2.32 (6.27)	-2.06 (6.13)	Condition: $F(1,21) = 4.006$, $p = .06$, $\eta_p^2 = .174$
Op 9	-1.65 (1.62)	-1.57 (1.47)	-4.03 (2.37)	-2.60 (1.92)	Region: $F(3,21) = 2.008$, $p = .07$, $\eta_p^2 = .182$
Op 10	.52 (5.40)	1.44 (8.50)	-2.80 (8.43)	-2.81 (7.30)	Group x condition = $F(1,21) = .042$, $p > .05$, $\eta_p^2 = .002$
Left PFC					
Op 5	3.52 (6.20)	2.26 (8.04)	2.75 (8.38)	-1.87 (3.43)	Group: $F(1,21) = 2.165$, $p > .05$, $\eta_p^2 = .100$
Op 6	.59 (1.20)	.49 (1.87)	-.49 (3.38)	-.49 (3.38)	Condition: $F(1,21) = .058$, $p > .05$, $\eta_p^2 = .003$
Op 11	3.94 (6.67)	5.13 (6.67)	-.33 (10.46)	.95 (10.11)	Region: $F(3,32) = 1.744$, $p > .05$, $\eta_p^2 = .084$
Op 12	-.32 (5.07)	-.53 (5.61)	-2.19 (10.41)	-.82 (10.59)	Group x condition = $F(1,21) = .011$, $p > .05$, $\eta_p^2 = .001$

Note: Abbreviations: MTF, multitasking framework; oxy, oxygenated; deoxy, deoxygenated; op, optode.

Various mixed MANOVA analyzing potential differences in haemodynamic response across the right PFC, medial PFC and left PFC revealed null results. On the right PFC, there were no significant within-group differences with the low and high difficulty conditions of the MTF for oxy-Hb change. Furthermore, no differences were observed among the optodes in the right PFC, suggesting that oxy-Hb levels in the region remained similar across the difficulty conditions. On the medial PFC, there was no effect of the MTF difficulty conditions on oxy-Hb change, but a statistical trend was apparent between the regional optodes, which contrasts show is because optode 3, located on the top-right side of the region, showed greater oxy-Hb decreases than the other channels. Moreover, there were no significant within-groups effects for oxy-Hb change in the left PFC on the MTF difficulty conditions or the optodes in the region. For between-groups analysis, there were no significant differences apparent in the right PFC, medial PFC or left PFC in oxy-Hb change (see Table 7.4 for MANOVA results), suggesting that modafinil users and nonusers experienced the same amount of cognitive workload on the MTF. Finally, there were no significant within or between-group interactions observable across any of the three PFC regions.

On the 3-back, several mixed MANOVA revealed varied results. There were no significant within-group differences for optodes covering the right PFC, medial PFC or left PFC. However, between-groups analysis revealed mixed findings, as there were no significant differences apparent between user groups and oxy-Hb change in the right and medial PFC. Nonetheless, there was a significant effect of user group on oxy-Hb change in the left PFC, which contrasts revealed was because users generally experienced an increase in oxy-Hb while nonusers had a decrease, a finding which suggests that users exerted more cognitive effort than nonusers. Lastly, there were no significant interactions apparent across the PFC regions (see Table 7.6 for MANOVA results).

Table 7.6 – Mean oxy-Hb change on the 3-back across the 12 optodes. Optodes are divided into the right PFC, medial PFC and right PFC as described in the previous table.

	Modafinil users	**Nonusers**	**MANOVA**
3-Back	**Oxy-Hb**		
	Mean (SD)		
	Right PFC		Results
Op 1	.08	-1.01	Group: $F(1,21) = 3.246$ $p = .06$, $\eta_p^2 = .176$
	(3.48)	(5.01)	
Op 2	-1.01	4.23	
	(5.01)	(10.62)	
Op 7	.43	4.97	Region: $F(3,21) = 3.073$, $p > .05$, $\eta_p^2 = .166$
	(4.57)	(3.54)	
Op 8	.22	2.52	
	(4.20)	(11.90)	
	Medial PFC		
Op 3	-.49	-2.50	Group: $F(1,21) = 2.701$, $p > .05$, $\eta_p^2 = .124$
	(4.87)	(6.71)	
Op 4	1.97	-2.87	
	(6.50)	(6.13)	
Op 9	-1.96	-2.81	Region: $F(3,21) = .944$, $p < .05$), $\eta_p^2 = .095$
	(1.53)	(2.38)	
Op 10	1.73	-3.98	
	(7.88)	(7.93)	
	Left PFC		
Op 5	2.33	-1.28	*Group: $F(1,21) = 7.268$, $p < .05$, $\eta_p^2 = .277$
	(6.09)	(3.63)	
Op 6	.12	-1.45	
	(1.27)	(4.30)	
Op 11	4.78	.04	Region: $F(3,21) = .284$, $p > .05$, $\eta_p^2 = .031$
	(6.99)	(8.70)	
Op 12	-.98	-3.39	
	(5.27)	(9.58)	

Note: * Significant at .05, **significant at .01, ***significant at .001. Abbreviations: MTF, multitasking framework; oxy, oxygenated; op, optode.

7.4.4 Blood Pressure and HRV Analysis

Table 7.7 shows average SBP, DBP and high and low frequency HRV for long-term modafinil users and nonusers across the cognitive tasks. For blood pressure analysis, mixed MANOVA revealed that there was a highly significant within-groups effect of MTF difficulty condition on SBP (see table 7.7 for within-groups results). Moreover, contrasts showed that both tasks significantly raised SBP when compared with baseline, and that the MTF hard condition significantly raised SBP higher than the MTF easy condition. Furthermore, there was a significant between-groups effect ($F(1,21) = 4.356$, $p < .05$, $\eta_p^2 = .295$) which contrasts revealed was apparent during completion of the MTF low and high conditions, as nonusers had significantly higher blood pressure than users. Findings for DBP were similar, within-groups analysis revealed a significant effect of the cognitive tasks, although contrast analysis showed that while the MTF easy and hard conditions had significant increases from baseline, they did not differ from each other. However, unlike SBP, there was no significant between-groups effect ($F(1,21) = 1.367$, $p > .05$, $\eta_p^2 = .098$) or condition x user group interaction ($F(1,21) = .943$, $p > .05$, $\eta_p^2 = .057$), suggesting that DBP was not influenced by user status. On the *3*-back, MANOVA also revealed a highly significant within-groups effect of the task on SBP, with contrasts showing that SBP was higher during the *3*-back than baseline. Again, there was no between-groups effect ($F(1,21) = 1.319$, $p > .05$, $\eta_p^2 = .101$) or interaction ($F(1,21) = .522$, $p > .05$, $\eta_p^2 = .016$) suggesting that user status did not impact SBP. Finally, there was no significant within-groups effect on DBP, nor was there a between-groups effect of user group ($F(1,21) = .229$, $p > .05$, $\eta_p^2 = .016$) or a significant interaction ($F(1,21) = .803$, $p > .05$, $\eta_p^2 = .024$).

Table 7.7 – Average SBP, DBP and high frequency HRV for long-term users and nonusers at baseline and during the cognitive tasks.

	Modafinil Users	Nonusers	MANOVA *F*
Systolic blood pressure	**Mean (SD)**		**Within-Groups Results**
Systolic Blood Pressure			
Baseline	110.69 (9.35)	116.50 (10.26)	
MTF Low	114.69 (10.29)	122.88 (10.97)	***MTF = $F(2,21)$ = 10.495, $p < .001$, $\eta_p^2 = .295$
MTF High	118.77 (7.46)	130.00 (14.57)	
3-back	116.08 (9.47)	120.63 (15.79)	**3-back = $F(1,21)$ = 5.413, $p < .01$, $\eta_p^2 = .191$
Diastolic Blood Pressure			
Baseline	71.00 (9.60)	73.63 (11.52)	
MTF Low	75.77 (5.93)	79.00 (12.15)	*MTF = $F(2,21) = 3.541$, $p < .05$, $\eta_p^2 = .097$
MTF High	73.77 (8.23)	80.25 (8.94)	
3-back	73.23 (9.61)	75.63 (11.46)	3-back = ($F(1,21) = .1.480$, $p > .05$) , $\eta_p^2 = .015$
High Frequency Heart Rate Variability			
Baseline	.155 (.19)	.30 (.37)	
MTF Low	3.99 (7.59)	1.61 (3.17)	MTF = $F(2,21) = 2.962$, $p > .05$, $\eta_p^2 = .044$
MTF High	2.83 (9.34)	5.80 (15.48)	
3-back	15.99 (33.13)	16.98 (28.30)	*3-back = ($F(1,21) = 5.314$, $p < .05$) , $\eta_p^2 = .170$

Note: * Significant at .05, **significant at .01, ***significant at .001. Abbreviations: MTF; Multitasking framework; low, low difficulty; high, high difficulty.

Heart rate variability analysis was conducted with high frequency data, which increased sensitivity to detect parasympathetic changes. A mixed MANOVA comparing HRV across MTF difficulty conditions found no significant within-groups effect. Contrasts revealed that participants had greater HRV on the MTF difficulty conditions than baseline, but, unexpectedly, there were no differences between the difficulty conditions themselves. Furthermore, there was no between-groups effect between users and nonusers apparent ($F(1,21) = .015$, $p > .05$, $\eta_p^2 = .007$), nor was there a significant condition x user group interaction ($F(1,21) = .949$, $p > .05$, $\eta_p^2 = .058$), indicating that HRV was not impacted by long-term modafinil use. Lastly, MANOVA comparing HRV on the 3-back from baseline found a significant effect, and contrasts showed that HRV was greater during the task than at baseline. Again, there was no significant between-groups effect of user group on HRV ($F(1,21) = .007) = p > .05$, $\eta_p^2 = .002$) and no apparent interaction ($F(1,21) = 1.049) = p > .05$, $\eta_p^2 = .032$), indicating that the 3-back task was the only variable which influenced HRV.

7.4.5 fNIRS Connectivity Analysis

Partial correlations comparing each channel on the MTF low difficulty condition between user groups are presented in Table 7.8, while partial correlations on the MTF high difficulty are shown in Table 7.9, and partial correlations on the 3-back are presented in Table 7.10. Correlation coefficients represent the relationship between two channels while controlling for any potential second order effects of the 10 other channels. Heat maps illustrate the connectivity between channels, with coefficients in red shades showing positive relationships and those in blue showing negative.

Table 7.8 – Partial correlation matrices depicting connectivity across the 12 channels in users and nonusers on the MTF low difficulty condition. Coefficients are presented in a heat map for greater visual illustration.

MTF Low Difficulty Modafinil Users

	OP1	OP2	OP3	OP4	OP5	OP6	OP7	OP8	OP9	OP10	OP11	OP12
OP1	1											
OP2	0.217	1										
OP3	-0.015	0.242	1									
OP4	-0.082	-0.141	0.068	1								
OP5	-0.045	-0.078	0.033	0.059	1							
OP6	-0.075	-0.115	-0.021	0.251	-0.258	1						
OP7	0.138	0.052	-0.007	0.007	0.246	0.137	1					
OP8	-0.005	-0.191	0.091	-0.166	-0.054	0.163	0.038	1				
OP9	-0.071	0.101	-0.008	-0.158	-0.087	-0.106	0.101	0.061	1			
OP10	0.059	0.024	0.088	0.190	0.051	0.060	-0.071	0.337	-0.382	1		
OP11	-0.057	0.018	0.137	0.001	0.349	-0.023	-0.028	0.055	0.183	0.005	1	
OP12	0.029	0.003	0.008	0.002	0.007	-0.024	-0.001	0.011	0.028	-0.001	-0.032	1

MTF Low Difficulty Nonusers

	OP1	OP2	OP3	OP4	OP5	OP6	OP7	OP8	OP9	OP10	OP11	OP12
OP1	1											
OP2	0.215	1										
OP3	-0.052	0.449	1									
OP4	0.016	-0.085	0.115	1								
OP5	0.032	0.143	-0.030	0.072	1							
OP6	-0.054	-0.030	0.188	0.145	-0.115	1						
OP7	0.173	0.196	-0.077	0.055	0.046	0.087	1					
OP8	0.173	0.021	-0.024	0.157	0.092	0.252	-0.163	1				
OP9	0.065	0.158	-0.101	-0.023	-0.035	0.082	0.022	-0.050	1			
OP10	-0.053	-0.052	0.166	0.252	0.074	-0.011	0.082	0.024	-0.160	1		
OP11	-0.039	-0.132	0.289	-0.091	0.229	-0.071	-0.042	-0.170	-0.135	0.083	1	
OP12	-0.060	0.062	-0.059	0.078	-0.031	-0.056	-0.646	-0.021	0.031	0.031	0.130	1

Channel connectivity between users and nonusers on the MTF low difficulty condition was similar, though some differences were apparent (See Table 7.8). In general, with both groups, positive correlations were highest in adjacent channels, or channels located in the same region (i.e., channels within the medial PFC), while negative correlations tended to be strongest in optodes further apart and in different regions (i.e., between the left and right PFC), although there were some exceptions. In both groups, there was visible connectivity in the right PFC, with channels 1 and 2 and channels 1 and 7 being moderately positively correlated. Interestingly, there were group differences visible with left PFC connectivity, as nonusers exhibited moderate positively correlated connectivity in channels 11 and 12, while users showed a minor negative correlation. Nonetheless, with both groups, channels 11 and 5, located in the left PFC, were moderately positively correlated. However, the biggest group difference was apparent between channels 7 and 12 which are in the right and left PFC, respectively. While users showed no connectivity between the channels, nonusers exhibited a strong negative correlation, which suggests that there was a significant difference in how the left and right PFC interacted during the task between user groups.

Table 7.9 – Partial correlation matrices depicting connectivity across the 12 channels in users and nonusers on the MTF high difficulty condition. Coefficients are presented in a heat map for greater visual illustration.

MTF High Difficulty Modafinil Users

	OP1	OP2	OP3	OP4	OP5	OP6	OP7	OP8	OP9	OP10	OP11	OP12
OP1	1											
OP2	0.216	1										
OP3	-0.091	0.262	1									
OP4	0.095	-0.026	0.003	1								
OP5	-0.001	0.152	0.132	0.141	1							
OP6	-0.087	-0.023	-0.134	0.223	-0.084	1						
OP7	0.023	-0.029	-0.063	0.108	0.042	0.203	1					
OP8	-0.035	-0.025	-0.040	-0.015	0.022	0.041	-0.184	1				
OP9	-0.075	0.044	0.002	-0.097	0.154	-0.115	0.288	0.069	1			
OP10	0.074	-0.100	0.130	0.143	0.057	0.037	0.100	0.440	-0.425	1		
OP11	0.101	0.055	-0.082	0.001	0.288	0.017	-0.007	-0.005	-0.036	0.118	1	
OP12	-0.085	0.009	-0.031	0.020	0.025	-0.028	0.042	0.046	-0.058	-0.032	-0.061	1

MTF High Difficulty Nonusers

	OP1	OP2	OP3	OP4	OP5	OP6	OP7	OP8	OP9	OP10	OP11	OP12
OP1	1											
OP2	0.253	1										
OP3	0.122	0.193	1									
OP4	-0.182	-0.100	-0.016	1								
OP5	0.053	0.395	0.013	0.062	1							
OP6	0.042	-0.077	0.096	0.160	-0.319	1						
OP7	0.170	0.152	-0.076	0.005	0.105	0.207	1					
OP8	0.003	0.010	-0.257	-0.071	-0.117	0.130	-0.002	1				
OP9	0.179	-0.075	-0.143	-0.199	-0.141	-0.125	0.092	-0.211	1			
OP10	0.193	0.067	-0.011	0.258	-0.072	0.053	-0.111	0.160	-0.338	1		
OP11	0.014	-0.041	-0.207	-0.147	0.177	-0.067	-0.154	-0.130	0.150	0.267	1	
OP12	-0.037	-0.022	-0.004	-0.042	-0.009	0.001	0.042	-0.114	0.011	0.026	0.009	1

On the MTF high difficulty condition, channel connectivity appeared to diverge between user groups (see Table 7.9). Overall, users experienced moderate and high positively correlated connectivity between optodes, whereas nonusers showed greater negatively correlated activity. In nonusers this suggests a haemodynamic trade-off, in that as oxy-Hb increased in some regions it was met by a decrease in others. With users, greater oxy-Hb increases across channels suggests greater cognitive workload during the task. However, groups were similar in some regards, particularly with adjacent channels, where several notable positive correlations were apparent (e.g., channels 2 and 3, channels 4 and 5 and channels 10 and 11). Optodes in specific regions also showed less connectivity in general. In the left PFC, channels 11 and 12 were uncorrelated in nonusers and negatively correlated in users; however, channels 5 and 6 in the same region were moderately negatively correlated in nonusers and appeared to lack correlation in users. Most notable was the medial PFC, where channels 9 and 10 were moderately negatively correlated in nonusers and strongly negatively correlated in users. There was also cross regional connectivity apparent in users, where channels 8 and 10, located in the right PFC and left PFC respectively, had a strong positive correlation.

Table 7.10. – Partial correlation matrices depicting connectivity across the 12 channels in users and nonusers on the 3-back. Coefficients are presented in a heat map for greater visual illustration.

3-Back Modafinil Users

	OP1	OP2	OP3	OP4	OP5	OP6	OP7	OP8	OP9	OP10	OP11	OP12
OP1	1											
OP2	0.223	1										
OP3	-0.078	0.294	1									
OP4	0.012	-0.111	0.144	1								
OP5	0.036	-0.036	0.009	0.148	1							
OP6	0.024	-0.111	-0.009	0.251	-0.013	1						
OP7	0.207	0.047	-0.109	-0.061	0.039	0.125	1					
OP8	-0.045	0.055	-0.036	-0.057	-0.126	0.162	-0.108	1				
OP9	0.047	0.025	0.086	-0.003	0.028	0.038	0.299	0.142	1			
OP10	0.003	-0.121	0.051	0.195	0.151	0.014	0.177	0.379	-0.497	1		
OP11	0.109	0.034	0.130	0.104	0.546	-0.087	0.045	0.025	-0.073	-0.115	1	
OP12	0.016	0.035	0.018	0.036	-0.070	-0.035	0.031	-0.029	0.001	0.040	0.023	1

3-Back Nonusers

	OP1	OP2	OP3	OP4	OP5	OP6	OP7	OP8	OP9	OP10	OP11	OP12
OP1	1											
OP2	0.375	1										
OP3	0.278	0.110	1									
OP4	0.050	-0.105	-0.148	1								
OP5	0.098	-0.016	-0.228	-0.093	1							
OP6	0.160	-0.158	-0.050	0.146	-0.235	1						
OP7	0.124	0.017	0.012	-0.034	0.177	-0.021	1					
OP8	0.249	-0.188	-0.231	0.046	0.062	0.190	-0.206	1				
OP9	0.169	0.198	-0.214	-0.109	-0.139	0.035	0.129	-0.011	1			
OP10	0.130	0.069	-0.123	0.292	-0.101	-0.065	0.208	0.183	-0.402	1		
OP11	-0.073	0.166	0.179	0.001	0.458	0.079	-0.170	-0.082	0.142	0.266	1	
OP12	0.007	0.010	-0.002	0.020	0.004	-0.007	0.001	0.012	-0.003	-0.004	-0.008	1

On the 3-back, connectivity also seemed to diverge between user groups (see Table 7.10). Channels tended to be more negatively correlated within nonusers, though to a lesser extent than seen on the MTF high difficulty condition. In nonusers, channels 9 and 3, both located in the medial PFC, were negatively correlated with more channels than users, although in both groups, channels 9 and 10 were highly negatively correlated, suggesting decreased activation of the medial PFC during the task. The left PFC showed greater activation in users than nonusers, as channels 11 and 5 were highly correlated among users but not with nonusers. Cross regional connectivity was also visible between the left and medial PFC in nonusers, as channels 9 and 10 were moderately correlated with channel 1. In users these channels showed weak and moderately negative correlations, suggesting that increases to right PFC activation was met with a trade-off in decreased medial PFC activity. Overall, users appeared to exhibit greater activation during the task than nonusers, particularly in the left PFC.

7.5. Discussion

Findings from this study do not support the hypotheses outlined earlier in the Chapter. Contrary to expectations, modafinil users did not exhibit differences in bilateral activation to the left and right DLPFC during any of the MTF difficulty conditions. However, connectivity analysis did show that during the MTF high difficulty condition, users experienced a general increase in oxy-Hb across multiple regions of the prefrontal cortex which was not apparent in nonusers. Furthermore, on the *3*-back, users showed increased activation of the left PFC compared with nonusers, but this finding was not specific to the DLPFC as predicted. Connectivity analysis also revealed that users experienced strong connectivity between channels 11 and 5 which are situated in the left PFC, which supports

findings from the main fNIRS analysis. There were also no observable group differences in high-frequency HRV or DBP, although, unexpectedly, nonusers had significantly higher SBP pressure during the tasks than users. Moreover, regardless of user group, fNIRS failed to detect general oxy-Hb change between participants in the MTF difficulty conditions. Furthermore, high-frequency HRV showed that R-R interval significantly increased from baseline on the cognitive tasks, but there were no differences during the MTF difficulty conditions. The same was found with DBP, which showed a modest increase from baseline and no task differences. Nonetheless, SBP revealed a linear increase, as all cognitive tasks significantly raised blood pressure from baseline with the MTF high difficulty raising it more than the low difficulty. Additionally, while it was predicted that modafinil users would perform worse on the cognitive tasks than nonusers, on the MTF high difficulty the opposite was found to be true, as users outperformed nonusers, which analysis showed was due to a better performance on the Stroop task. Finally, against expectations, user groups did not differ in response to the subscales of the NASA-TLX, suggesting that there were no self-reported differences in perceived workload. As such, none of the hypotheses in this study could be accepted.

Despite findings opposing predictions, differences in haemodynamic response between user groups reveal some neurophysiological differences which are in line with previously discussed research. Similar to findings from Montgomery et al. (2017) with ecstasy poly-drug users, modafinil users showed greater oxy-Hb change during the *3*-back despite showing a similar performance to nonusers. While, ostensibly, it may appear that a comparable performance on the *3*-back suggests that modafinil users did not exhibit cognitive deficits in working memory, increased oxy-Hb in the left PFC, a region previously shown to govern working memory functions, suggests that users invested greater cognitive effort to achieve similar behavioural output to nonusers. This finding does appear to support the notion that, like illicit stimulants, long-term modafinil use may result in working

memory deficits. However, the same was not found during the MTF, as haemodynamic response was similar across the PFC between user groups, yet modafinil users exhibited improved performance compared with nonusers on the high difficulty Stroop. This is like findings from Study 2 which revealed quicker response rates on the cued go/no-go task for modafinil users which further suggests that they show improved response inhibition when compared with non-using controls. It may then be that while the drug might be detrimental to certain cognitive functions, improvements to inhibitory control and reaction time suggest that it might ameliorate others. It should be noted, of course, that users did not perform better on the visual warning task, itself a test of attention and reaction time. As such, this finding could instead indicate that modafinil users make use of their cognitive resources more effectively, by focusing on tasks they find more manageable to meet the demands of the test. This may also explain why SBP was significantly lower in users than nonusers, particularly since blood pressure differences were most apparent during the MTF high difficulty condition. As modafinil users appeared to make better use of their resources, it stands to reason that they became less stressed than nonusers which reduced SBP.

7.6 Chapter Summary

In this chapter, haemodynamic response, HRV and blood pressure changes during completion of the *3*-back working memory task and a multitasking stressor have been explored in modafinil users vs. healthy controls. Furthermore, this study is the first to address long-term modafinil use by examining the potential neurophysiological and psychophysiological impact of use. Use of fNIRS revealed potential working memory deficits in modafinil users who completed the *3*-back, and blood pressure measurements showed users had lower SPB on all tasks. Furthermore, users also outperformed nonusers on the high difficulty Stroop, showing that, as was also demonstrated in Study 2, users

appear to have better inhibitory control. As such, this study revealed that while modafinil users appeared to demonstrate better performance in some areas, deficits may be apparent in others. Taken together with the previous study, modafinil appears to impact cognitive performance in ways which were not anticipated. Overall, CE strategies have been comprehensively explored, and long-term use of the most popular PCE drug, modafinil, has been found to have some effect on cognitive performance and haemodynamic response. The final chapter attempts to fully extrapolate the implications of the 3 studies which make up this thesis and places them in context with pre-existing literature.

Chapter 8: General Discussion.

8.1 Thesis Summary

The principal aim of this thesis was to investigate the use of cognitive enhancement drugs. It also aimed to: (1) investigate the aetiology of CE use in select UK universities, (2) assess the effects of long-term modafinil use on executive functioning, (3) explore the effects of long-term modafinil use on neurophysiological processes, and (4) examine the relationship between changes in cognitive performance and neurophysiological reactivity, to determine if neurovascular activation could be used as a proxy for cognitive workload. The first Chapter examined which substances are purported to enhance cognitive functioning, and these were defined as either 'soft enhancers' or 'PCE' based on product type and pharmacology. An examination of prevalence estimates found that the stimulant modafinil appeared to be the most popular PCE for study at university. Consequently, Chapter 2 explored modafinil use in healthy and clinical populations, to determine what impact the substance has on cognitive performance, if it is an effective PCE, and its side effects and potential harms. It was concluded that although short-term use (< 3 months) was deemed to be relatively safe when administered as part of clinical studies, there was no available data on the safety and cognitive impact of non-clinical and longer periods of use (> 3 months). Chapter 3 examined the most appropriate methods of detecting changes in cognitive workload, an umbrella term for measuring different aspects of cognitive performance in response to task difficulty, in long-term users of modafinil. This review showed that the most appropriate way was a mixture of subjective, cognitive and neurophysiological methods. Chapter 4 described the methods chosen in the later empirical studies, and outlined the theoretical frameworks which underpinned them, including why a survey methodology is best for collecting demographic and drug use data with substance using populations, and how fNIRS, ECG and blood pressure measurements

can be used as indicators of neurophysiological changes associated with increased cognitive workload.

The three empirical studies which followed used various methods to explore CE use in the UK. Study 1 (Chapter 5) described a survey of CE use in university students, including the substances used, and the predictors of use. Use of substances for CE was predicted by age (being older), gender (being male), and believing use of modafinil for CE to be more morally acceptable predicted soft enhancer and PCE use. In keeping with previous research, modafinil was the most popular PCE drug among respondents, and so subsequent studies examined this drug. Study 2 (Chapter 6) examined cognitive performance across a range of executive functions which have been shown to improve with acute modafinil (as reviewed in Chapter 2), including working memory, sustained attention and inhibitory control. Due to the neurochemical similarities between modafinil and other psychostimulants like cocaine, it was hypothesised that long-term users would show poorer performance in these cognitive functions compared with non-using controls. This hypothesis was not supported, and modafinil users showed faster response times to all cues on the cued go/no-go task without demonstrating an accuracy trade-off, and there were no other performance differences between groups on the remaining tasks. Therefore, Study 3 (Chapter 7) built on these findings by adding neurophysiological measures to examine underlying mechanisms, and to see if long-term modafinil use, like other psychostimulants such as cocaine, was also associated with negative neurological and physiological effects during high-demand cognitive performance. The tests undertaken by participants were more cognitively challenging than the previous study and working memory and multitasking capacity was assessed. Like Study 2, modafinil users demonstrated better inhibitory control which was expressed on the high difficulty Stroop when compared with non-users, but they showed greater oxy-Hb change on the *3*-back, despite no differences in performance on the task.

Heart rate variability was not statistically different between groups across the tasks, but SBP was consistently lower in modafinil users.

8.2 Discussion of Findings

Study 1 made numerous predictions regarding patterns of CE use, including: (H^1) use of soft enhancers would generally be higher than PCE, (H^2) modafinil would be the most popular PCE drug for study purposes, (H^3) reported use of illegal drugs for study would be smaller than soft enhancers and PCE, but recreational use would be higher than PCE, and (H^4) sociodemographic and personality factors would predict use, specifically: Gender (being male), age (being older) level of study (being a postgraduate), learning style (being a surface learner) and moral perceptions of PCE use (H^4). Consequently, all hypotheses, beside the H^4, were supported by the data, and observed levels of CE use generally supported previous research (Maier et al., 2013; Singh, Bard, & Jackson, 2014a; Wolff, Brand, Baumgarten, Lösel, & Ziegler, 2017). Perhaps the most unsurprising finding was the general popularity of soft enhancers containing caffeine. Coffee and energy drinks had the highest levels of lifetime use regardless of user intent, followed by caffeine pills. The greater popularity of soft enhancers over PCE seems to be due to these caffeinated products. Nutraceutical use was modest, and use of bacopa, ginkgo and guarana for study was lower than PCEs, especially modafinil use. In this study, Modafinil use was comparable to levels previously reported in the UK (Holloway & Bennett, 2012; Singh et al., 2014a), excluding the recent study by Maier and colleagues which suggested a recent and significant rise in use of the drug in the UK from 2015 to 2017 (Maier, Ferris & Winstock, 2018). The popularity of modafinil was important for several reasons. As discussed in Chapter 2, the pharmacological similarity of modafinil with other psychostimulants highlights a public health concern if UK students are using stimulants as a study aid. Furthermore, without robust data on long-term effects of use of modafinil, public health

education cannot be provided. The popularity of modafinil is also important for universities to consider, as the use of substances to cope with study demands may reflect poor student support or issues with student working practices or workload. It may be that this finding highlights a need for universities to address PCE use as part of university policy, to make it clear that alternative coping methods are available and provide balanced health education on these substances. Nevertheless, level of modafinil use was still below what was previously suggested in the media (Lennard, 2009; The Student Room 2016) and in Maier and colleagues' (2018) recent study. One reason might be that region of the country played a role in the results, as the study described in this thesis looked at use in four Northern universities only, and did not take account of user rates in the South of England or other parts of the UK as other studies did. Use might also be higher at specific universities, particularly those "elite" universities which form the Golden Triangle. This would explain reports by Varsity, a University of Cambridge newspaper which reported that 10% of students were using modafinil. It is possible that demands on students are higher at these institutions because of academic expectations, and students might be more likely to use techniques like PCE to aid them in study to achieve a good grade. Of course, the opposite could also be true and students at these universities might be more academically capable and could rely less on external aids such as PCE for study. However, it should be noted that study 1 included a Russell Group university, where there could arguably be a similar demand on students. Nonetheless, differences in use seen between studies may come as a combination of these factors.

Previous research has also suggested that a number of variables were associated with greater CE use, including; being male and over 25 (Maier et al., 2016; Maier et al., 2018), working alongside study (Maier et al., 2016), being a final year undergraduate or in postgraduate study (Maier et al., 2013) and perceiving CE use to be more morally acceptable (Maier, Liakoni, et al., 2015). As a consequence, it was hypothesised that several

factors could form a predictive model, although screening analyses examining correlational relationships excluded some of the variables described from further exploration to avoid impairing the predictive ability of the final regression solution. This is contrary to previous studies, which clearly indicated that many of these factors were linked to CE use. The lack of predictive capability might therefore come as a result of the study being exploratory, as some variables were thought suitable for analysis without direct evidence of their impact on CE use. This was because it was determined that they could add to student stress, such as semester-time accommodation, or whether a student has a deep or surface approach to learning (see Chapter 5). Perhaps these exploratory variables are not perceived to contribute to student stress as much as anticipated, or perhaps stress is not a driving factor in use of these substances in the first place. Nevertheless, the variables remaining in the logistic model successfully predicted CE use. The most powerful predictor of PCE use was gender, as being male made use significantly more likely. This is also a common finding in prior research across Europe (Maier et al., 2016; Maier et al., 2018), so it is unsurprising that the same was found here. Being older also predicted greater use of all CE categories, perhaps due to the increased academic rigour/workload older people can expect as they progress through study. It was also unsurprising that moral perception of modafinil use predicted PCE and soft enhancer use. This might also reflect the popularity of modafinil in the UK, with users of the drug likely to have a more positive attitude to its use and a better attitude to the use of other strategies like soft enhancers. Nevertheless, it is interesting that moral perceptions of d-amphetamine and MPH did not predict use, although this is likely because, so few respondents reported using these substances in general. A higher response rate to the survey might have revealed a link between moral perception of these substances and CE use, as was demonstrated by Maier et al. (2015) in Swiss university students' attitudes towards PCE use.

Several predictions were made for Study 2: including (H^5) that modafinil users would perform worse on cognitive performance measures than nonusers, (H^6) more frequent modafinil use would also predict poorer performance on the cognitive performance measures, as would greater poly-drug use and recent use of illicit stimulants and cannabis, and (H^7) modafinil use would be significantly correlated with greater levels of poly-drug use reported by participants in the modified Background Drug Use Questionnaire. However, findings indicate that long-term modafinil use does not appear to have the same impact on cognitive performance, which was predicted due to its similar neurochemical properties to illegal stimulants. In fact, decreased response time to all cues on the cued go/no-go task implies that the drug may have extended benefits beyond initial periods of use, as it suggests that users were able to process stimuli and respond quicker. Chapter 2 already highlighted the cognitive benefits conferred from acute modafinil use, and studies indicate that in healthy people inhibitory control performance is enhanced (Marchant et al., 2009; Rycroft et al., 2007; Turner et al., 2003). However, the question remains as to why such improvements are observable after at least 48 hours of abstinence from the drug. This could be explained by methodological issues pertaining to the use of a cross-sectional survey. For instance, due to the scarcity of modafinil users in Study 2 and 3, drug use frequency and average dose could not be accurately assessed. It is possible that use was too infrequent for a true behavioural impact of long-term use of the drug to be recorded. Therefore, it might be that findings are less attributable to modafinil use and more aligned with personality type or another factor which can be linked to long-term users. Additionally, as statistical modelling in Study 1 successfully identified factors associated with PCE use, it appears intuitive to think along these lines. It has been reported that PCEs are commonly used to gain a competitive edge (Maier et al., 2015), as such, users of this drug might simply be more competitive than nonusers, and they could be more accustomed to competitive tasks like cognitive performance measures. Nevertheless,

performance was not significantly different in working memory or sustained attention, which discredits the notion that they are better across all performance measures. It is also possible that continued modafinil use leads to long-term changes in neurology and cognitive function in a similar way to how SSRIs alter certain forebrain structures over time (Haddjeri, Blier, & de Montigny, 1998). Even after cessation, antidepressants show some positive outcomes to behaviour and cognition (Amado-Boccara et al., 1995). The same could be true with modafinil, although a lack of robust data showing consistent use of the drug with the sample makes this a strenuous comparison, particularly since SSRI's are often taken daily.

In Study 3, modafinil use was examined using fNIRS to assess neurovascular coupling in the prefrontal cortex as a proxy of cognitive workload. It was predicted that: (H^{8}), modafinil users would exhibit differences in haemodynamic response which would occur bilaterally in the left and right DLPFC indicating increased cognitive effort compared with controls during the cognitive performance measures, (H^{9}) differences would also be observed in HRV and BP with users showing reduced HRV and elevated BP compared to nonusers, (H^{10}) all participants would exhibit increased oxy-Hb change and blood pressure as well as a significant reduction in HRV relative to baseline during the cognitive tasks, (H^{11}) and modafinil users would perform significantly worse on the cognitive performance measures than nonusers and also report greater mental workload on the NASA-TLX. In this study, findings were less consistent than Study 2, and although inhibitory control was better in users on the high difficulty Stroop, increased oxy-Hb change in users on the *3*-back despite no behavioural differences implies an underlying deficit in working memory. Haemodynamic findings therefore contradict the notion that modafinil provides only long-term improvements to cognitive functioning, and it may be that while inhibitory control is better, it comes at a cognitive trade-off to working memory performance. Moreover, working memory deficits are typical with repeat cocaine administration (Jovanovski, Erb, &

Zakzanis, 2005), as such the previous comparisons made between modafinil and other psychostimulants are pertinent. Furthermore, Study 3 also took account of blood pressure and HRV measurements, and although HRV was not significantly different between user groups, modafinil users generally had lower SPB than nonusers during all cognitive performance measures, suggesting that, physiologically, they coped better with the demands of the tasks. This could relate to the earlier suggestion that users are more accustomed to acting competitively than nonusers, and as a consequence they become less physiologically stressed during the cognitive performance measures. Furthermore, another interesting finding is that although users performed better on the high difficulty Stroop, when results are scrutinised it appears that users simply sustained strong performance between the low and high difficulty conditions, whereas nonusers demonstrated a significant decline at the harder difficulty. This may suggest that users are better at sustaining cognitive performance under challenging tasks than nonusers in general, and not simply in inhibitory control. Furthermore, there were no within-group differences between the different MTF difficulty conditions, which is surprising as previous research using the same task configuration has shown difficulty related performance differences (Wetherell & Carter, 2014). However, on closer inspection of performance on the visual warning and visual tracking tasks, users and nonusers improved their scores on the harder difficulty variants. One explanation could be that because in both instances the time required to respond to each task was far shorter during the harder difficulty, participants attended more closely to these tasks, which improved their scores. This could also explain why nonusers scored significantly lower on the high difficulty Stroop, as they were less effective at distributing their cognitive resources than modafinil users. Finally, it should be noted that there were no group differences on responses to the NASA-TLX, and despite the behavioural and neurophysiological differences, users did not differ to nonusers in perceived workload. This suggests that although some performance differences were

visible, participants did not indicate this during self-reporting. As such, this reflects that users did not acknowledge the increase in cognitive effort displayed on the *3*-back which was visible due to the observed oxy-Hb increase, which indicates a lack of awareness.

8.3 Methodological Strengths and Limitations

The research described in this thesis makes several unique contributions. First, Study 1 explored level of CE use and also looked at associated factors of use, including sociodemographic and educational variables. At the time of writing, this is the first study to attempt to form a predictive model of use which successfully highlighted gender, age and moral perception as variables significantly correlated with soft enhancer and PCE use, and also illustrated those factors which appear to be unrelated to use. Both Study 2 and 3 were also unique in that long-term modafinil users have not been cognitively tested previously. Chapter 2 demonstrated that prior research had explored acute modafinil use in different populations quite comprehensively, but until now no data existed with use exceeding 3 months. Consequently, cognitive performance measures and use of multiple neurophysiological measures made a comprehensive psychophysiological assessment of modafinil use which had not been done previously. The strengths of this research programme are therefore linked to the novelty of the studies conducted.

Throughout this thesis, several methodological decisions were made which have inherent limitations. Primarily, in Study 1, it should be highlighted that national university prevalence could not be estimated because the sample was self-selected and thus cannot be taken as true representation of PCE use at UK universities. Furthermore, estimates were not necessarily fully representative of the participating universities, particularly since response rates for two institutions were quite limited (EM1: N = 18, NE1: N = 44), making it

possible that users, or indeed nonusers, were disproportionately represented. Due to potential sampling biases, the study could over-represent CE users, as these respondents may have felt more compelled to participate in a survey investigating substance use behaviour at university than nonusers. Indeed, the opposite could also be true, and due to the novel nature of using PCE for study, and because of possible stigmas associated with use, respondents may also have been dishonest about use. However, to reduce false responses, participants were explicitly informed that responses were fully anonymous. Moreover, participants could have completed the survey more than once, particularly to increase chances of winning in the prize draw. Nonetheless, data was checked for response duplicates and matching IP addresses to minimise the chances of this occurring before analysis was conducted. Lastly, memory biases must be considered with an extensive self-report measure like this one, as the survey requested quite specific information about past substance use, which may have been difficult to recall leading to inaccuracies in responding.

Studies 2 and 3 also share a number of limitations because of a similar methodology with sampling and investigating drug use behaviour. First of all, substance use was self-reported with the modified Drug Use Questionnaire as researchers did not have access to a clinical sample of people prescribed modafinil daily, which could have assured consistent use of the drug. As such, like in Study 1, the research was vulnerable to participants inaccurately reporting, or deliberately misrepresenting, their drug use behaviour. This could be a result of memory problems, as the questionnaire relied on quite specific drug taking information, including exact time periods and quanities, which may have been difficult to recall. Furthermore, the threshold for inclusion in the long-term modafinil user group was limited to only once per month use for at least a year. This is mainly due to the overall novelty of the substance, and that modafinil is less popular than other stimulants such as caffeine (as shown in Study 1), making people who use more frequently difficult to obtain as

participants. For instance, in Study 2, the average user reported using 5.74 pills a month, which is considerably less than a daily dosing schedule. It could therefore be the case that use was not frequent enough in the sample to observe any further cognitive deficits, changes to HRV and blood pressure which are typically found with chronic stimulant use, or indeed potential benefits. In Study 2, modafinil users also reported using significantly more of other types of substances over the previous 3 months than nonusers, although there were no significant correlations between modafinil use in the previous year and other substance use variables. Therefore, it must be acknowledged that modafinil users were more likely to be general polydrug users, making it difficult to determine how the current findings were attributed just to modafinil use and not polysubstance use more generally. Despite this, correlational analysis did also reveal that modafinil users did not report greater use of alcohol, illegal stimulants or cannabis use than controls, suggesting that these drugs did not impact performance on the behavioural measures. In Study 3, due to the relatively limited availability of modafinil users during the time of data collection, the sample was not robust enough to perform regression analysis and look at the impact that frequency of use, and other potentially important factors such as poly-drug use, might have on neurophysiology. Limitations withstanding, this study is the first of its kind to assess the long-term impact of modafinil use on psychophysiology and neurophysiology. Furthermore, despite some drawbacks with the sample, this research is the first to demonstrate increased cognitive effort in modafinil users as a compensatory mechanism for what appears to be a working memory deficit.

8.4 Future Research Implications

The studies presented here include findings which could be further examined in future research. The survey study did show that, as predicted, modafinil was the most popular PCE drug, but it did not confirm Maier and colleagues (2018) recent findings of 10% user

rates in the sample. Of course, both studies used self-selected sampling which does not represent true user prevalence, it is therefore necessary to establish which figures more accurately represent use, and this could be achieved with a largescale survey study which takes account of prevalence in universities across different regions of the UK. Instead of relying on a self-selection, future studies should obtain a representative sample of UK students, which is randomly selected and takes account of different sociodemographics (i.e., age, ethnicity). Furthermore, future research should continue to establish a predictive model of use, looking at factors which are already known to be associated with use, such as gender and morality, and which also investigate unexplored variables. As educational and sociodemographic variables in Study 1 which were thought to contribute to stress did not predict CE use, perhaps personality measures might have greater predictive capability. Personality traits have been intricately linked to substance use behaviour. Perhaps one of the most highly regarded measures of personality traits is the Five-Factor Model (McCrae & John, 1992), which describes five personality dimensions: openness to experience, conscientiousness, extraversion, agreeableness and neuroticism. Furthermore, extraversion and openness have strong links to alcoholism (Martsh & Miller, 1997) and substance misuse (Terracciano, Löckenhoff, Crum, Bienvenu, & Costa, 2008), but neither of these scales have yet to be used to examine CE use. A model examining these factors might successfully predict CE use, and thus identify characteristics which could make students more inclined toward CE strategies.

Future lab-based research with modafinil users should also make some considerations. As average monthly frequency of modafinil use varied within the cohort of users for both Study 2 and 3, there was no doubt a certain degree of unexplained variance attributed to this. As such, access to a clinical sample could minimise this variance and might provide a more accurate picture of the drug's impact on behavioural and neurophysiological functioning by implementing a longitudinal design which follows participants across a

course of treatment. In Study 2, modafinil use was also found to be associated with poly-drug use. It is unknown what impact the use of other substances had on cognitive performance, therefore any future study should try to recruit a sample with no recent history of other substance use, so that any potential effects can be more confidently attributed to modafinil use. Challenges may come as a result of recruiting such a specific sample of users, although a research programme which does not suffer the same time and resource constraints as a PhD may find this more attainable. Furthermore, research should attempt to replicate some of the findings from the studies described here, including the demonstrated improvements in inhibitory control without a speed/accuracy trade off, and the apparent underlying deficits to working memory processes. A different multitasking set-up might also improve on findings, as the inclusion of the visual warming and visual tracking tasks, and how participants attended more closely to these windows in the higher difficulty conditions, made differences in over-all scores between conditions non-significant. The MTF allows for a change in the tasks which occupy the 4 windows, as such it could be useful to replace the current set-up with more tasks assessing working memory and inhibitory control. Finally, future research should attempt to find a gender balance in the sample, as it was a challenge in these studies to find an equal proportion of female modafinil users. It is unclear how much of an impact gender had on the results of Study 2, but a more equally distributed sample might reveal gender differences as a factor effecting performance.

8.4.1 Implications for Policy and Practice

Beyond academic research, the persistent nonmedical use of PCE substances, particularly among students at university, leaves several considerations for policy and practice. Principally, university and government bodies must first work together to consider a collective strategy when tackling PCE use, taking into consideration not just potential for

harm and abuse, but also prospective neuroethical implications. Several countries already prohibit possession of pharmaceutical substances without prescription (including the UK and USA), with possession often punishable under the law (Petersen & Petersen, 2019). Nevertheless, little is done to consider, or indeed understand, possession of these substances as study drugs. The findings from the studies described in this thesis outline the intricacies of this topic. Regardless of legality, the findings from Study 1, and literature discussed in Chapter 1, reveal that although use is not widespread, it is still prevalent. If legal status is therefore not sufficient to deter use, then a new approach must be sought. Study 3 indicated an underlying working memory deficit among modafinil users, although further research is required to fully establish this effect. Thus, if later findings corroborate this and other potential drawbacks, then policy and practice must respond accordingly. Increased access to health information regarding such drugs should be a primary objective, no less since PCE's are poorly understood even among academics. As such, a drug information campaign targeting universities is essential if students are to make informed decisions about PCE use. Of course, difficulties arise when attempting to monitor use as universities are not sufficiently equipped to police students in this way, nor should this be the sought approach. Instead, institutions should set their gaze on what is driving students to these substances and should take steps to accommodate personal study needs. Chapter 1, and the introductory section of Chapter 5, outlined that stress and perceived workload are common reasons provided by students for their PCE use. Consequently, effort should be taken to address these concerns at an administrative level, perhaps by increasing student outreach and making university-based counselling services widely available.

From an ethical point of view, study benefits, and indeed grades, conferred by PCE raises issues of deservingness. Arguably, academic achievements born of these methods are less deserving of recognition than those without. If growing evidence suggests that PCE use continues to increase, then universities must thoroughly explore the accompanying ethical

implications, particularly if academic performance differences (i.e., better grades) become noticeable between users and nonusers. It is beyond the remit of this thesis to make moral claims regarding PCE use, thus no attempt has been made to do so. Nevertheless, universities should be prepared to ask these questions, to fully explore whether these methods are compatible with an academic ethos, and whether integrity is lost due to PCE use.

8.5 Conclusions

This thesis aimed to explore PCE use in UK university students and made several unexpected but important findings. Results indicate that long-term modafinil use is similar to effects seen with illegal stimulants in some ways, but markedly dissimilar in others. Furthermore, this study programme has taken a novel approach to PCE research, and findings with modafinil users reveal complexities which must be examined with future research to be better understood. It also appears that it is too reductionist to simply predict that modafinil exerts a similar long-term impact to other pharmaceutical or illegal stimulants without considering the drug's unique neurochemical properties. Furthermore, in terms of how these findings translate to a real-world context, this thesis has revealed that although PCE use was shown to be modest, it does exist within UK universities. Thus, questions are raised for institutions on how to tackle the use of pharmaceuticals and whether to make additional provisions for students so that these techniques do not rise in prevalence and become a study norm. Furthermore, long-term nonmedical modafinil use must also be closely monitored, both in and outside university. Findings reveal mixed effects on cognitive performance and haemodynamic change, and this thesis shows that research with long-term use of this substance is still too premature to fully determine if modafinil is harmful or safe. Therefore, a lack of knowledge does not equate to the absence of harm, and the mixed findings from these studies show that public health information

should be provided to stem growing use until it is better understood. Consequently, findings from this thesis are encouraging, and reveal that there is still more to understand about the broad topic of PCE use if student use is to be properly addressed.

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Appendix

Moral judgement:

Sally

Sally's exams are quickly approaching, and she is struggling to find the time to study. Sally has a part-time job to help pay her rent and works four evenings a week. This only leaves her with three available study days, but by Sally's own admission, she is often too tired to revise on these days off. Sally's friend, Sarah, understands that she is short of study time and suggests that Sally try modafinil, a prescription drug that will help her to stay awake and focused long enough to study. Sarah recommends the drug because she has used it in the past to help her revise for her own exams, and she says it has even helped her to achieve top marks. Sarah has some modafinil left over, and even offers to give it to Sally.

1. Sally should use the modafinil offered to her by Sarah.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

2. It is right for Sarah to offer Sally modafinil as a study aid.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

3. **Taking modafinil will give Sally an unfair academic advantage**.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

4. **Sally is cheating if she takes modafinil to help her study.**

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

5. It doesn't matter what techniques Sally uses to study only that she gets good grades.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

6. The ends justify the means.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

7. It doesn't matter how beneficial they are as a study aid, taking drugs is wrong.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

Simon

Simon is in the final year of his undergraduate studies. Throughout his time at university, he has consistently used the drug Adderall, a substance that increases focus and alertness, to help him complete his assignments and study for exams. Simon kept his Adderall use a secret, as he feared that it would be viewed as cheating by his peers and by the university. But, when his classmate Claire recently asked for his advice on how to achieve higher grades, he told her all about his Ritalin use, and recommended it to her as a study aid. Unexpectedly, however, Claire was unhappy with Simon, and called him a cheater, and even reported him to the faculty for academic misconduct.

1. Simon is wrong to have used Adderall for so long during his studies.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

2. Claire did the right thing to report Simon for academic misconduct.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

3. Simon should have continued to keep his Adderall use a secret.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

4. Claire is right, Simon is a cheater.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

5. It's right that Simon is charged with academic misconduct.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

6. Simon should be allowed to use Adderall as a study aid if he wants.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

7. It is immoral to use Adderall or any other substances as a study aid.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

John

John doesn't believe in using brain enhancing drugs to get ahead a university and has repeatedly told his peers that he thinks it is cheating. He has never struggled with his studies, despite having multiple commitments, such as a part time job and a family. However, his son has recently been diagnosed with ADHD, which has proved to be a difficult time for John and his family. As a result, John's studies have begun to get on top of him, and he has found it more and more difficult to keep up with the academic rigour. Tomorrow is a deadline for an important assignment, and John has barely even looked at the course material. If he doesn't submit something, he will surely fail the module, and this could jeopardise his entire degree. However, if he takes his son's ADHD medication, Ritalin, on just this one occasion, then he will have the focus to complete the assignment.

1. John should bend the rules this once and take Ritalin to help him complete his assignment.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

2. John is betraying his own values if he takes Ritalin.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

3. There's nothing wrong with using Ritalin as a study aid just once.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

4. John should maintain his values even if he failures his assignment

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

5. John's difficult family situation justifies the use of drugs as a study aid.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

6. John is cheating if he takes Ritalin.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

7. Taking Ritalin is a hypocritical thing for John to do.

Strongly disagree	Disagree	Moderately disagree	Agree nor disagree	Moderately agree	Agree	Strongly agree

How difficult was it to answer these questions?

Very easy	Easy	Moderately easy	Neither easy nor difficult	Moderately difficult	difficult	Very difficult