The Effect of Modafinil on Behavioural and ERP Correlates of Inhibitory
Control in Healthy, Non-Sleep Deprived Individuals

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Statement of Sources

I declare that this report is my own original work and that contributions of others have been duly acknowledged.

_____________________________  Date: _______________________

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The Effect of Modafinil on Behavioural and ERP Correlates of Inhibitory Control in Healthy, Non-Sleep Deprived Individuals

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Abstract

Modafinil is a novel wakefulness-promoting medication that has become popularised for purposes of cognitive enhancement. Research has indicated that modafinil may improve inhibitory control-related functioning, though to date no studies have attempted to explore these effects using electrophysiological methods. This study investigated the effect of 200mg of modafinil on behavioural (RT and accuracy) and electrophysiological (N2 amplitude) correlates of inhibitory control within a sample of 18 healthy, non-sleep deprived males aged 19-27 years. Participants completed pre- and post-ingestion versions of a Flanker Go/Nogo paradigm over two double-blind, placebo-controlled experimental conditions. Results indicated that while modafinil maintained baseline levels of mood, sleepiness and alertness to a significantly greater extent than placebo, no effect on inhibitory control processes was observed on RT, accuracy, or amplitude of the N2 component. Despite this, tentative evidence was found for an overall improvement in processing speed following modafinil ingestion, independent of inhibitory control processes. Future research is necessary to investigate these effects further, and determine the extent to which they manifest independently from fatigue-inducing environments.
Modafinil is a novel wake-promoting agent, or eugeroic, intended for use in the treatment of excessive daytime sleepiness. First developed in the early 1990s and licensed in Australia in 2002, modafinil is presently approved by the Therapeutic Drug Administration as a Schedule-IV prescription treatment for narcolepsy, chronic shift-work sleep disorder, and obstructive sleep apnoea (TGA, 2008). Despite this, recognition of a low abuse liability and lack of adverse effects has led to modafinil being utilised for a range of off-label indications, including depression, attention-deficit/hyperactivity disorder, multiple sclerosis, and chronic fatigue (Farah, Smith, Ilieva, & Hamilton, 2014; Minzenberg & Carter, 2008). Notably, modafinil use has emerged among healthy populations as a means of pharmaceutical neuroenhancement: the use of pharmaceutical substances for the targeted enhancement of cognitive, affective and motivational function (Repantis, Schlattmann, Laisney, & Heuser, 2010). Commonly recognised as a nootropic or ‘smart drug’, modafinil is often considered in context with other popular pharmacological neuroenhancers, including caffeine, piracetam, methylphenidate and dexamphetamine.

An informal online poll conducted by Nature has indicated that the most common demographic using modafinil and other cognitive enhancing agents were those aged from 18 to 25, with the primary purpose being to improve concentration or focus for specific tasks (Maher, 2008). Use among other groups has also popularised modafinil as a cognitive enhancer, with reports of surgeons using modafinil for purposes of combating fatigue and loss of concentration (Franke et al., 2013), and US air force pilots, for whom modafinil has been approved for use on missions lasting longer than 12 hours (Repantis et al., 2010; USAF, 2004). The increasing exposure of modafinil for these purposes has consequently led to an
extensive body of research aimed at investigating the potential cognitive enhancing effects of modafinil among both sleep-deprived and well-rested populations, with emphasis on areas of attention, memory, learning, and executive functions. In particular, a number of studies have indicated that modafinil may enhance processes related to inhibitory control. To date, however, no studies have attempted to utilise temporally precise techniques such as event-related potentials (ERPs) to investigate effects of modafinil on this specific cognitive process.

**Neurochemical Effects and Mechanisms of Action**

Despite the increasing usage and off-label applications of modafinil, the mechanism by which modafinil may produce wakefulness-promoting and cognitive enhancing effects is yet to be conclusively identified (Qu, Huang, Xu, Matsumoto, & Urade, 2008). Although frequently associated with amphetamines due to its wake-promoting properties, it is now recognised that the pharmacological profile and behavioural effects of modafinil are distinct from other psychostimulants, indicating a unique mechanism of action (Minzenberg & Carter, 2008). To date, there is strong evidence that the direct modulation of catecholamine transporters, specifically norepinephrine and dopamine in areas of the prefrontal cortex and hypothalamus, are primary to the wakefulness enhancing effects of modafinil (de Saint Hilaire, Orosco, Rouch, Blanc, & Nicolaidis, 2001; Madras et al., 2006; Qu et al., 2008). Secondary to catecholamine effects, extracellular reductions in GABA and elevations in serotonin, glutamate, orexin, and histamine systems are also observed, again with particular prominence in neocortical areas relative to subcortical structures (Minzenberg & Carter, 2008). The apparent role of catecholamine modulation at prefrontal sites has consequently fuelled interest regarding the effects of modafinil on aspects of attention and executive functions.
Attention, Executive Functions and Inhibitory Control

Given that the enhancement of selective attention, concentration, and inhibition of distraction is a primary motivator for many people seeking both modafinil and other forms of cognitive enhancement (Maher, 2008), investigating the influence of modafinil on executive functions and particularly inhibitory control has become a key focus of many studies. Petersen and Posner’s (2012) model of the attentional system states that in addition to both the alerting and orienting networks, executive functions form one of the three primary systems of the attentional network. Executive functions encompass a set of top-down cognitive processes involved in the selection and manipulation of incoming information, and are commonly associated with higher-order functions such as planning, decision-making and adaptive reasoning. Diamond’s (2013) model of executive functions states that these higher-order functions derive from the interactions of three core executive processes: inhibition, working memory, and cognitive flexibility. Inhibition, or inhibitory control, hence constitutes an integral component of the executive system, and primarily involves the ability to inhibit irrelevant information and focus attention or behaviour towards more goal-directed or appropriate action.

Inhibitory control is itself further subdivided into facets of behavioural inhibition and cognitive inhibition or selective attention (Diamond, 2013). Behavioural inhibition, or ‘self-control’, involves the resistance of temptation or impulsivity to making prepotent responses. In a behavioural sense, inhibitory control aids in inhibiting or overcoming a dominant response, often in order to perform a subdominant one. In this way, behavioural inhibition allows individuals to avoid common errors of impulsivity and instead formulate more measured or intentional responses. Cognitive or attentional inhibition, by contrast, acts as a mediator of
attentional distribution, enabling selective attention to particular stimuli whilst suppressing interference from others. Also referred to as focused attention, this form of inhibition or attentional control enables the voluntary inhibition of certain environmental stimuli based on current goals or intentions of attending (Diamond, 2013).

**Modafinil in Healthy, Sleep Deprived Individuals**

The cognitive enhancing effects of modafinil following sleep-deprivation have been extensively researched, particularly given the status of modafinil as a wakefulness-promoting agent. Studies in this area have largely focused on more general effects of wakefulness and maintaining performance on ecologically valid tasks, such as flight simulators in military personnel (Repantis et al., 2010). However, enhancement of executive functions has also been investigated, primarily due to the negative effects that sleep deprivation may have on these processes, and their importance in daily functioning (Wesensten, 2006).

A systematic review by Repantis et al. (2010) examined the efficacy of modafinil for neuroenhancement across 31 studies pertaining to both sleep-deprived and non-sleep deprived populations. Neuroenhancement was investigated in relation to attention, mood, memory, wakefulness, and executive functions. In studies on sleep deprived individuals, they reported that single dose administration produced large improvements in wakefulness ($d=2.6$), memory ($d=1.22$), and executive functions ($d=3.3$), with no significant effects on attention or mood. Effects on executive functions were indicated to be very strong and persistent over time, though this was not observed for repeated administration studies involving long periods of sleep-deprivation, where only wakefulness was modulated by modafinil (Repantis et al., 2010).
As an integral part of the executive system, processes of inhibitory control are evidently implicated in any enhancement of executive functions. In a simulated night shift study (n=32), 200mg of modafinil was found to significantly enhance alertness, vigilance, and performance on tasks of executive functions and inhibitory processes (Walsh, Randazzo, Stone, & Schweitzer, 2004). Participants who had been administered modafinil, showed significant improvements on the Maintenance of Wakefulness Test and Psychomotor Vigilance Test. Enhanced performance was also observed in the Wisconsin Card Sorting Test and Haylings Sentence Completion Test; two tests involving executive functions and response inhibition. Further evidence for enhancement inhibitory processes in sleep-deprived populations is evident in a study by Wesensten, Killgore and Balkin (2005), in which 400mg of modafinil following 85 hours of sleep deprivation countered performance impairments on the Stroop task, suggesting modafinil effectively maintained processes of selective attention and interference inhibition.

**Modafinil in Healthy, Non-Sleep Deprived Individuals**

While Repantis et al. (2010) demonstrated effects of cognitive enhancement, and particularly enhancement of executive functions, following modafinil administration in moderately sleep-deprived individuals, they propose that the extent of these effects remains equivocal in well-rested populations. In studies pertaining to healthy, non-sleep deprived individuals, only moderate enhancements on attention (d=.56) were observed, with insufficient data to investigate effects on executive functions. Review of the current literature largely reflects these conclusions, as studies investigating the effects of modafinil on aspects of attention, executive functions and inhibitory control in samples of healthy, non-sleep deprived individuals, have largely produced mixed results.
In a double-blind, between subjects design, Turner et al. (2003) compared placebo to single doses of 100mg and 200mg of modafinil on an extensive battery of neuropsychological tests. In their sample of 60 healthy males, modafinil was shown to improve performance on tasks of digit span, visual pattern recognition, and spatial planning. Additionally, on the Stop-Signal paradigm, improvements in inhibitory control functions were indicated by both significantly reduced stop-signal reaction times (RTs) and significantly reduced error rates, suggesting modafinil both increased accuracy through the inhibition of reflexive responding whilst also increasing the efficiency and speed of the response (Turner et al., 2003). While dosage-dependent effects were not observed in other tasks, reduced stop-signal RTs and error rates were found for participants on 200mg of modafinil relative to those on 100mg. These findings were among the earliest to provide evidence for the enhancing effects of modafinil on executive functions, indicating a potential effect of selective enhancement of inhibitory control processes in healthy individuals.

These effects, however, have not been so clearly replicated in ensuing studies. In a between-subjects design, Randall, Shneerson, Plaha, and File (2003) found no effects of modafinil on cognitive performance across a battery of neuropsychological tests in 30 healthy, non-sleep deprived students. Tasks included tests of working memory, spatial planning, sustained attention, and response inhibition, and revealed no differences between placebo, 100mg, and 200mg modafinil groups. In a following study, Randall, Fleck, Shneerson, and File (2004) again observed few effects of modafinil on performance in a battery of neuropsychological tests, this time within a sample of 45 non-sleep deprived, middle-aged participants. A significant effect of modafinil was, however, observed on reduced time taken to complete the Stroop task for participants on 200mg of
modafinil, though this was observed only for the congruent, colour-naming component of the Stroop task, and not the incongruent word-naming component in which inhibition resources are necessary.

Due to the relatively small sample sizes of these studies and potential lack of power to detect to significant effects between groups, a third study by Randall, et al. (2005b) again examined effects of modafinil on a neuropsychological test battery among 60 young, non-sleep deprived individuals. In addition to greater performance on tasks of digit span, pattern recognition, and a rapid visual information processing (RVIP) task of sustained attention; participants who ingested 200mg of modafinil also replicated previous findings of greater performance on the congruent component of the Stroop task (Randall et al., 2004; Randall, et al., 2005b). Again, these results provide little support for the role of modafinil in enhancing processes of inhibitory control, such as those demonstrated by Turner et al. (2003). Rather, enhancement processes appeared to be limited to enhanced sustained attention, indicating an effect of enhanced early processing or general vigilance, potentially as a result of combating day fatigue (Randall, et al., 2005b).

While the effect of modafinil on enhancing behavioural correlates of inhibitory control in healthy, non-sleep deprived individuals remains unclear, imaging research has indicated that modafinil may have an impact on cortical activity within areas implicated in inhibitory control processes. While Rasetti et al. (2010) found no differences in performance on a Variable Attentional Control (VAC) task, fMRI analysis did indicate a significant decrease in BOLD signal within the anterior cingulate cortex (ACC) following 100mg modafinil ingestion relative to when participants ingested placebo. The VAC task involves focusing on arrows of three different sizes, with varying degrees of inhibitory control mediated by the
congruency of the cued target arrow with the direction of flanking arrows. Task load is increased from low, moderate to high depending on the size and congruency of the cued arrow in relation to its flankers. Despite observing no significant differences in accuracy or RT; increasing task load was associated with greater activation in the ACC for participants on placebo relative to modafinil. The ACC is an area richly innervated by catecholeminergic neurons, and is frequently implicated in executive functions including inhibitory control (Rasetti et al., 2010). A decrease in activity within the ACC during modafinil conditions was suggested to indicate increased cortical efficiency, with fewer resources necessary to attain similar levels of performance achieved in placebo conditions.

Given that relatively low, 100mg doses of modafinil were used in this study, it is possible insufficient doses may account for the absence of behavioural differences on the VAC task, particularly since previous research has identified dosage-dependent effects in similar tasks (Turner et al., 2003; Wesensten, 2006). Additionally, the small sample of 11 participants to complete the VAC may have also presented problems with power sufficient to detect significant differences between conditions.

Despite this, similar patterns have emerged from fMRI research by Minzenberg, Watrous, Yoon, Ursu, and Carter (2008), comparing prefrontal cortex (PFC) and locus coeruleus activity during a Preparing to Overcome Prepotency (POP) task of attentional inhibition and cognitive control. Similarly, while no effects on RT and accuracy were seen across the sample (n=22), significant task-dependent increases in PFC activity and PFC-LC functional connectivity were observed following ingestion of 200mg of modafinil relative to placebo. Similar to the ACC, these areas are considered to encompass catecholaminergic systems highly
implicated in functions of inhibitory and cognitive control. In a later study utilising the same POP task in conjunction with EEG, modafinil was also demonstrated to enhance oscillatory power in theta, alpha, and beta ranges at frontal and parietal electrode sites (Minzenberg et al., 2014). These middle frequency cortical oscillations have been implicated in a number of aspects of executive functioning, with alpha oscillations in particular considered to be associated with attentional, task-focused inhibition (Jensen & Mazaheri, 2010; Minzenberg et al., 2014).

Although no significant effects on POP task performance were observed in either the fMRI or EEG study, methodological limitations in these designs may account for the lack of apparent effects. Ceiling effects were problematic in both studies, and as a result behavioural effects of modafinil may have been more difficult to discern (Minzenberg et al., 2014; Minzenberg et al., 2008). For instance, Minzenberg et al. (2008) noted significant improvements in accuracy on incongruent POP trials in a sub-sample of 11 below-ceiling performers during the modafinil condition. Furthermore, repeated administration of the POP task in the EEG-based study resulted in practice effects occurring independently of drug and placebo condition, and as a result may have consequently concealed otherwise discernible effects of the drug (Minzenberg et al., 2014). When overall RT to both congruent and incongruent trials was compared across task blocks, significant decreases in RT were observed for modafinil but not placebo conditions (Minzenberg et al., 2014).

In a recent systematic review on the cognitive enhancing effects of modafinil in healthy, non-sleep deprived populations, it was argued that methodological discrepancies throughout the literature likely account for a substantial proportion of the inconsistent findings (Battleday & Brem, 2015). In their review of 24 studies pertaining to processes of executive functions, attention, learning, memory and
creativity; Battleday and Brem (2015) reported that within studies utilising basic
testing paradigms, enhancements of executive functions are frequently observed,
though improvements in attention, learning and memory are seen to a lesser degree.
When complex assessment paradigms are used however, modafinil is suggested to
consistently enhance processes of attention, learning and executive functions.
Complex tasks are described as novel paradigms developed for the assessment of
higher order functions and global cognitive domains, as opposed to the direct
assessment of specific sub-functions, such as inhibitory control.

Battleday and Brem (2015) suggest that the complexity of task paradigms
utilised in studies attempting to identify neuroenhancement is a major factor in the
detection of significant effects. Given that many of the paradigms were originally
developed for clinical populations, ceiling effects become an issue when attempting
to investigate enhanced performance in healthy populations. The effect of ceiling
performance in placebo controls also offers some explanation as to why
electrophysiological or imaging techniques may reveal group or condition-based
differences in the absence of differences in behavioural performance (Minzenberg et
al., 2014; Minzenberg et al., 2008; Rasetti et al., 2010). Battleday and Brem (2015)
argue that in studies assessing performance on novel and more complex tasks,
cognitive enhancing effects of modafinil are more readily observable. Issues with
this approach do arise however, given that novel and complex tasks are often less
well standardised than the ‘simple tasks’ critiqued within the review, and typically
provide less evidence on effects of specific and well-described functions such as
inhibitory control.
Electrophysiological Correlates of Inhibitory Control

There remains a substantial lack of research utilising electrophysiological techniques to examine the potential effects of modafinil on enhancement of cognitive processes, particularly in healthy, non-sleep deprived individuals. Given the extensive, yet equivocal research surrounding the effect of modafinil on processes of inhibitory control, the utilisation of more temporally precise measures may provide further insight regarding the extent to which modafinil may specifically enhance these processes.

Event-related potentials (ERPs) allow for the investigation of neural correlates of particular cognitive processes with high temporal resolution, enabling neural activity to be tracked on a scale of milliseconds (Pires, Leitao, Guerrini, & Simoes, 2014). The anterior N2 component is a negative deflection that peaks approximately 200-350ms post-stimulus onset, and has been suggested to be modulated by functions of cognitive and executive control (Folstein & Van Petten, 2008). In particular, the anterior N2 component is proposed to index processes of frontal inhibitory control, suggested to derive from areas of the PFC and ACC (Falkenstein, 2006; Folstein & Van Petten, 2008). The classical paradigm in which these effects are observed is the Go/Nogo task, in which participants must respond to one class of stimuli and withhold response to a second class of stimuli. Greater N2 amplitude is hence observable on the ‘nogo’ trials of response inhibition, referred to as the nogo-N2 effect (Falkenstein, 2006). The Eriksen flanker task is also a common paradigm used to elicit the N2 component, by which participants respond to a central letter surrounded by either congruent, identical letters, or incongruent letters that differ from the target. Again, greater N2 amplitude is observed on trials where participants must inhibit interference of incongruent ‘flanking’ letters (Heil, Osman,
Wiegelmann, Rolke, & Hennighausen, 2000). The combined Flanker Go/Nogo paradigm incorporates aspects of both tasks, with enhanced N2 amplitude observable on both congruent nogo trials and incongruent go trials relative to congruent go trials. In this paradigm, the N2 component is particularly enhanced on incongruent, nogo trials, where both inhibition of flanker interference and inhibition of response are necessary (Heil et al., 2000).

In populations where inhibitory control deficits are thought to occur, reduced N2 amplitude is observed when utilising these paradigms. Johnstone, Barry, Markovoska, Dimoska, and Clarke (2009) demonstrated that in children with ADHD, significantly reduced N2 amplitude is observed during nogo trials of the Go/Nogo task, and to incongruent stimuli of the Flanker task, relative to children in the control group. Similar findings have also been demonstrated in chronic cannabis users, where significant reductions in N2 amplitude on nogo, and particularly nogo incongruent trials on the Flanker Go/Nogo paradigm, were observed relative to drug naive controls (Nicholls, Bruno, & Matthews, 2015). The effect of modafinil on the N2 component remains an unexplored issue, with no studies to date attempting to utilise ERPs to investigate effects in this area.

**Rationale, Aim and Hypotheses**

Given the varying evidence for the enhancing effect of modafinil on inhibitory control processes in healthy, non-sleep deprived populations, the present study aims to specifically elucidate the effect of modafinil on this primary executive function. As fMRI and EEG research has indicated effects may occur neurologically in the absence of apparent behavioural differences (Minzenberg et al., 2014; Minzenberg et al., 2008; Rasetti et al., 2010), the present study intended to expand upon previous literature by utilising ERP techniques to acquire temporally precise
indices of an inhibitory control mechanism. The present study used a Flanker Go/Nogo paradigm due to being a well standardised measure of inhibitory control and effective in elicitation of the N2 component. In consideration of task complexity and ceiling effects, task difficulty was maximised through brief stimulus presentations and the utilisation of phonologically and visually similar target and distracter stimuli.

In sum, it was therefore the aim of the present study to utilise a Flanker Go/Nogo paradigm to investigate the effect of a 200mg dosage of modafinil on both behavioural and ERP correlates of inhibitory control in a sample of healthy, non-sleep deprived individuals. Specifically, differences in RT, accuracy, and amplitude of the anterior N2 component were compared across conditions influenced by either a single-dose of modafinil or placebo.

It was firstly hypothesised that on the Flanker Go/Nogo paradigm, participants would exhibit significantly slower reaction times (RTs) for incongruent stimuli relative to congruent stimuli. If modafinil does enhance inhibitory control processes, it is expected that at post-ingestion testing, this increase will be significantly reduced in participants under the modafinil condition relative to the placebo condition. The second hypothesis was that across go/nogo trial types, a significant reduction in accuracy would be observed for incongruent stimuli relative to congruent stimuli. Again, if modafinil enhances inhibitory control, this reduction is expected to be significantly less for participants under the modafinil condition compared to placebo conditions at post-ingestion testing. The final hypothesis was that the increase in N2 amplitude between go and nogo trials (nogo effect) was expected to be significantly greater for incongruent stimuli relative to congruent stimuli. Again, if modafinil enhances inhibitory control, this enhancement of N2
amplitude is in turn expected to be significantly greater for participants under the modafinil condition relative to the placebo condition.

**Method**

**Participants**

An a priori power analysis indicated that a sample of nineteen participants were sufficient for the detection of a moderate effect size ($f = .25$) at a power of 0.8. Nineteen male participants aged 19-27 were recruited for the study. One participant was excluded due to not completing both sessions, resulting in a final sample of 18 participants.

Exclusion criteria included: being female; any use of illicit drugs in the past month or a history of frequent use; regular tobacco use; current use of any prescribed medications; any current neurological, physical or psychological conditions; alcohol dependence or abuse as measured by the Alcohol Use and Disorders Identification Test (AUDIT; Babor, Higgsens-Biddle, Saunders, Monteiro, 2001; defined as scores $\geq 16$); high levels of psychological distress as measured by the Kessler Psychological Scale (K10; Kessler, 2002; defined as scores $\geq 30$); risk of psychosis as identified by the Psychosis Screener (Degenhardt, Wall, Korten & Jablensky, 2005; defined as scores $\geq 1$) and the Schizotypal Personality Questionnaire-Brief (SPQ-B; Raine & Benishay, 1995; defined as scores $\geq 17$); and daily use of paracetamol or ibuprofen. Participants were also excluded based on a BMI lower than 18 and history of adverse reactions to caffeinated beverages. Fluent English was also a requirement due to the linguistic stimuli used in the cognitive task. Participants were asked to abstain from alcohol 24hrs prior to testing, and paracetamol and ibuprofen on the day of testing. Participants were asked to consume caffeine as normal, and to eat a light lunch prior
to arriving at the experimental session between 12pm and 1pm. It was also necessary that participants pre-organise transportation home for the end of each session.

Participants were recruited via advertisement around the University of Tasmania, peer referral, and advertisement to the first year psychology cohort (via SONA online research participation system). Interested applicants contacted researchers via SMS or email, and were contacted for a preliminary screening via telephone. Participants were reimbursed $80 for time and expenses, and first year psychology students had the option of either $80 reimbursement, or partial course credit and partial reimbursement. At the beginning of the first session, all participants were provided with an information sheet, and written informed consent was obtained (see Appendix A). The study was approved by the Tasmania Health & Medical Human Research Ethics Committee (see Appendix B).

Materials

Questionnaire Measures. A standardised screening questionnaire included questions pertaining to: demographic information; history of illicit drug use; tobacco use; current medications; history of neurological, physical or psychological conditions; caffeine consumption; BMI; first-spoken language; and handedness. An experimental session questionnaire (see Appendix C) was used at the beginning of each session, including questions pertaining to: recent caffeine, nicotine, alcohol, drug, and medication use; food consumption; hours slept; and measurement of BMI. A side effect checklist (see Appendix D) was provided at the end of each session, comprising a Yes/No checklist of commonly reported side effects (MIMS, 2009), and space to report any additional adverse effects.

The Alcohol Use and Disorders Identification Test (AUDIT; Babor et al., 2001) was used to identify problematic consumption of alcohol within the past 12
months, with scores $\geq 16$ indicating potential alcohol dependence. The AUDIT comprises 10 questions aimed at identifying hazardous alcohol use, alcohol dependence symptoms, and alcohol-related problems, and has demonstrated efficacy across age, gender and culture (Babor et al., 2001).

The Kessler Psychological Distress Scale (K10; Kessler et al., 2002) is a 10-item scale which was used to detect psychological wellbeing over the past 4 weeks. Questions regarding experiences of psychological distress were answered on a 5-point Likert scale ranging from 1 (none of the time) to 5 (all of the time), with scores of 30 or more indicating a very high level of psychological distress (ABS, 2007). The psychometric properties of the K10 have been validated for use across a range of sociodemographic samples (Kessler et al., 2002).

The Psychosis Screener (Degenhardt et al., 2005) is a brief 7-item measure used to identify features of psychotic disorders, with scores $\geq 1$ indicating potential psychosis. This was used in conjunction with the Schizotypal Personality Questionnaire-Brief (SPQ-B; Raine & Benishay, 1995), a 22-item scale in which scores $\geq 17$ indicate a disposition to schizotypal traits.

The Profile of Mood States-Short Form (POMS-SF; Shacham, 1983) was used as a pre- and post-ingestion measure of mood states. Ratings are provided on the subjective appropriateness of 37 different mood states using 5-point Likert scales ranging from ‘not at all’ to ‘extremely’. The scale consists of nine subscales, pertaining to Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigour-Activity, Fatigue-Inertia, and Confusion-Bewilderment. Total mood disturbance is calculated from the sum of all subscales, ranging from scores of 0-148.

The Karolinska Sleepiness Scale (KSS; Åkerstedt & Gillberg, 1990) is a 9-point measure of subjective sleepiness, and was used as a pre- and post-ingestion
measure during each session. The scale ranges from ‘extremely alert’ to ‘very sleepy, great effort to keep awake, fighting sleep’, with higher scores indicating a greater level of sleepiness.

The Weschler Test of Adult Reading (WTAR; Weschler, 2001) is a test of verbal intelligence comprising 50 irregularly spelled words of which participants are required to correctly pronounce. Final raw scores reflect the number of correctly pronounced words, and are converted to standardised scores based on age. Standardised scores correlate strongly with overall verbal IQ ($r = .75$) and full-scale IQ ($r = .73$; Weschler, 2001).

Visual Analogue Scales (VAS; see Appendix E) of Subjective Performance were used as pre- and post-ingestion measures in which participants mark a point along a 10cm continuum according to their extent of agreement with the item, ranging from ‘strongly agree’ to ‘strongly disagree’. Lower scores indicated greater levels of agreement with the item. Items related to feelings of alertness, confidence in performing cognitive tasks, and confidence in driving ability in each experimental session. VAS of Subjective Drug Effects were used post-ingestion in both experimental sessions, with items relating to strength of drug effect, liking of drug effect, alertness, and intoxication. Higher scores indicated a greater drug effect.

**Flanker Go/Nogo paradigm.** In the Flanker Go/Nogo paradigm (adapted from Nicholls, Bruno & Matthews, 2015), the Erikson flanker task (Eriksen & Eriksen, 1974) is combined with the go/nogo response paradigm. Within each trial, a fixation cross was first presented for 300ms, followed by a letter string comprising five white-font uppercase letters (subtending 2.0° x 8.0°) with a duration of 250ms. Inter-trial intervals ranged from 1550ms to 1950ms in 100ms increments. Participants were required to focus on the middle letter of each letter string stimulus
and respond with their left or right index finger upon presentation of a ‘B’ or ‘C’ stimulus (go trial), respectively. Participants were required to withhold their response upon presentation of a ‘D’ or ‘G’ stimulus (nogo trial). Centre letters of the letter-string stimuli were flanked with either congruent (BBBBB) or incongruent (DDBDD) distracter letters. Go versus nogo trials and congruent versus incongruent stimuli were each presented with equal probability. The experimental task in total comprised one practice block of 10 trials, and four experimental blocks of 100 trials each. At the beginning of each session, a shortened, 100-trial baseline task was administered in order to assess within-day behavioural performance from pre- to post-ingestion, and to control for practice effects across sessions.

**Electrophysiological (EEG) recording.** Cognitive tasks were presented on a computer using the NeuroSCAN Stim2 software. EEG activity was simultaneously recorded using the NeuroSCAN 4.54 system and a 32-channel Quik-Cap with Ag/AgCl sintered electrodes. According to the international 10-20 system of electrode placement, continuous EEG data was recorded from 32 sites at a rate of 1000Hz. Electrodes were referenced to linked mastoids, and electrode impedance was kept below 10kΩ. Horizontal electro-oculographic (EOG) activity was recorded from the outer canthi of both eyes, and vertical EOG activity recorded from above and below the left eye.

During editing, behavioural data was merged with continuous EEG files and subsequently filtered using a Zero-phase-shift low-pass filter (30Hz, 24dB/Oct). Ocular artefact reduction (via an artefact averaging and reduction procedure) was then performed to control the effect of eye blinks on other electrode channels. Data epochs were then extracted from 100ms before stimulus onset to 900ms post-stimulus. Baseline correction and artefact rejection was subsequently conducted, with
trials containing artefacts above 70 \( \mu V \) or below -70 \( \mu V \) removed. The fronto-central peak N2 component was determined from grand averaged waveforms and was defined as the maximum amplitude 240-360ms post-stimulus onset. An automatic peak detection process was then performed, followed by manual corrections.

**Randomisation and blinding**

To ensure blinding of participants and experimenters, the randomisation of drug condition was conducted by an independent researcher prior to the recruitment of any participants, and was determined by a randomisation schedule from randomization.com. Upon establishing eligibility, participants were assigned a unique code based on sequence of presentation, each of which corresponded to pre-packed envelopes determining order of drug condition over the two sessions. This order was counterbalanced across participants, so that half the sample would ingest modafinil in the first session, and the other half, placebo. Both modafinil and placebo capsules were matched for size, shape and colour, so that neither participants nor experimenters may discern differences. Modafinil capsules were each filled with gluten-free cornflower and a 100mg tablet of modafinil, whereas placebo capsules were filled only with gluten-free cornflower.

**Procedure**

After screening, eligible participants were invited to attend two experimental sessions at the University of Tasmania, over which they were tested under the influence of both placebo and 200mg of modafinil. All sessions began between 12pm and 1pm, and each lasted 4 hours. Within-participant sessions were separated by at least 1 week in order to control for any residual effects of modafinil if ingested during the first session. After providing informed consent at the beginning of the first session, participants underwent secondary screening to confirm eligibility. This
included completion of the AUDIT, the K10, the SPQ-B, the experimental session questionnaire, and measurement of BMI.

Participants then completed the POMS-SF, KSS, WTAR, VAS, and a shortened (100 trial) Flanker Go/Nogo baseline task. Subsequently, either 200mg of modafinil or placebo was administered (two capsules), as per the predetermined order. This was followed by a 2 hour interval prior to EEG setup, ensuring cognitive testing occurred during modafinil peak plasma levels, 2-4 hours post-ingestion (Minzenberg & Carter, 2008). During this break participants were able to relax in a private room where they could read, study or watch television, though were regularly checked on. At 2 hours post-ingestion participants underwent setup for EEG recording and were afterward seated in front of a computer, ready to begin testing at 2.5 hours post-ingestion. During cognitive testing, participants completed two tasks in counterbalanced order (one of which is not reported in the present study) lasting approximately 45 minutes in total. Participants were instructed to respond as quickly and accurately as possible whilst minimising eye and body movements. When finished, participants completed the post-ingestion POMS-SF, KSS and VAS, before being dismissed. At the end of their second session, participants received a complete debriefing and were reimbursed for their time and out-of-pocket expenses.

**Design and Data Analysis**

The data was assessed to ensure the assumptions of ANOVA had been met. Any individual RTs greater than 3 standard deviations above the participants’ mean were recognised as outliers and excluded from the analysis. An accuracy cut-off of less than 75% was used to determine outliers within the accuracy data, with no exclusions found to be necessary. Baseline measures and VAS of Subjective Drug Effects were compared using paired samples t-tests. The POMS-SF subscales, KSS,
and VAS of Subjective Performance were analysed using 2 (Drug Condition: modafinil, placebo) x 2 (Time: pre-ingestion, post-ingestion) repeated measures ANOVAs.

Behavioural dependent variables for the Flanker Go/Nogo task were RT (ms) and accuracy (% of correct responses). RT was analysed using a 2 (Drug Condition: modafinil, placebo) x 2 (Time: pre-ingestion, post-ingestion) x 2 (Congruency: congruent, incongruent) repeated measures ANOVA on correct ‘go’ trials of the task. Accuracy was analysed using a 2 (Drug Condition: modafinil, placebo) x 2 (Time: pre-ingestion, post-ingestion) x 2 (Trial Type: go, nogo) x 2 (Congruency: congruent, incongruent) repeated measures ANOVA. For the accuracy data, only significant or theoretically relevant non-significant main effects and interactions are reported.

The electrophysiological dependent variable was peak amplitude of the N2 component of the ERP waveform. Consistent with previous literature, preliminary analyses showed that N2 amplitude was maximal at frontal electrode sites, and analyses were restricted to the midline frontal site (Fz). Analysis of N2 amplitude was achieved using a 2 (Drug Condition: modafinil, placebo) x 2 (Trial Type: go, nogo) x 2 (Congruency: congruent, incongruent) repeated measures ANOVA.

Any significant interactions were followed up using Bonferroni corrected pair-wise comparisons in order to maintain a Type 1 error rate of less than 5%. Effect sizes were measured using partial eta squared ($\eta_p^2$) for any omnibus ANOVAs, and Hedge’s $g$ for any tests of simple effects. Magnitude of effect for Hedge’s $g$ was interpreted using Cohen’s (1992) convention of small (0.2), moderate (.05), and large (0.8), and for $\eta_p^2$, the convention of small (0.01), moderate (0.06) and large (0.14).
Results

Demographic and Screening Variables

Table 1 shows mean age, demographics and scores on questionnaire measures. Analysis of demographic and screening variables indicated that the sample were largely university educated, of average intelligence (as measured by the WTAR), and in a healthy weight range. Problematic alcohol use (as measured by the AUDIT), psychological distress (as measured by the K10), and risk of psychosis (as measured by the psychosis screener and SPQ-B) were all identified as within the low risk range.

Baseline Measures, Side Effects and Blinding

Variables with the potential to confound the results were compared at baseline between each drug condition and are displayed in Table 2. No significant differences were observed between the modafinil and placebo conditions on prior caffeine intake, hours of sleep the previous night, baseline sleepiness (as measured by the KSS), or baseline mood disturbance (as measured by the POMS-SF). McNemar tests were conducted on the proportion of participants to report each item on the side effect checklist, with no significant differences between the conditions. Four participants in the modafinil condition did, however, report additional adverse effects of minor shakiness; minor visual disturbance/hallucination while completing tasks; neck and jaw tension; and increased heart rate and breathing accompanied by shakiness. Follow up inquiry indicated that none of the participants found the symptoms to be severe or distressing, and no intervention was required.
## Table 1

*Means and Standard Deviations for Demographic and Screening Variables*

<table>
<thead>
<tr>
<th>Variable</th>
<th>M</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21.40</td>
<td>2.33</td>
<td>19-27</td>
</tr>
<tr>
<td>Level of Education (% completed Year 12)</td>
<td>100%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Level of Education (% commenced/completed tertiary)</td>
<td>88.9%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Handedness (% right handed)</td>
<td>83.3%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Caffeine Use (% ≥ 2 times per week)</td>
<td>77.7%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>BMI</td>
<td>23.0</td>
<td>4.20</td>
<td>18-34</td>
</tr>
<tr>
<td>Problematic Alcohol Use (AUDIT)</td>
<td>3.83</td>
<td>2.96</td>
<td>0-10</td>
</tr>
<tr>
<td>Psychological Distress (K10)</td>
<td>13.24</td>
<td>4.88</td>
<td>0-23</td>
</tr>
<tr>
<td>Risk of Psychosis (SPQ-B)</td>
<td>3.53</td>
<td>4.94</td>
<td>0-17</td>
</tr>
<tr>
<td>General Intellectual Functioning (WTAR standard score)</td>
<td>104.6</td>
<td>9.5</td>
<td>82-118</td>
</tr>
</tbody>
</table>

A Wilcoxin’s Signed Rank test on blinding indicated that confidence of ingesting modafinil was significantly higher in the modafinil condition (\(Mdn=50.0\%\)) relative to the placebo condition (\(Mdn=17.5\%\)), \(T=19.5, p=.021, r=-.054\). Confidence ratings were, however, highly variable between participants in both conditions, with ranges of 0% to 100% in the modafinil condition, and 0% to 80% in the placebo condition.
Table 2

*Means (Standard Deviations) and Paired Samples t-Tests for Control Variables at Pre-Ingestion and McNemar Tests for Reported Side Effects at Post-Ingestion*

<table>
<thead>
<tr>
<th>Control Variable</th>
<th>Modafinil (Mean, SD)</th>
<th>Placebo (Mean, SD)</th>
<th>t</th>
<th>p</th>
<th>g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine Intake (per drink)</td>
<td>.50 (.86)</td>
<td>.61 (.78)</td>
<td>.81</td>
<td>.430</td>
<td>.13</td>
</tr>
<tr>
<td>Prior Sleep (hours)</td>
<td>7.47 (1.06)</td>
<td>7.67 (1.22)</td>
<td>.73</td>
<td>.474</td>
<td>.17</td>
</tr>
<tr>
<td>Sleepiness (KSS)</td>
<td>4.72 (1.02)</td>
<td>4.67 (1.24)</td>
<td>.18</td>
<td>.859</td>
<td>.05</td>
</tr>
<tr>
<td>Total Mood Disturbance (POMS-SF)</td>
<td>17.72 (10.94)</td>
<td>17.06 (10.54)</td>
<td>.49</td>
<td>.634</td>
<td>.06</td>
</tr>
</tbody>
</table>

Side Effect Checklist

<table>
<thead>
<tr>
<th></th>
<th>Modafinil (%)</th>
<th>Placebo (%)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5.6%</td>
<td>16.7%</td>
<td>.625</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>0%</td>
<td>11.1%</td>
<td>.500</td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>38.9%</td>
<td>11.1%</td>
<td>.063</td>
<td></td>
</tr>
<tr>
<td>Runny Nose</td>
<td>0%</td>
<td>5.6%</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Sore Throat</td>
<td>0%</td>
<td>0%</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>11.1%</td>
<td>5.6%</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>16.7%</td>
<td>11.1%</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

*Note:* POMS-SF Total Mood Disturbance ranges from 0-148, with higher scores indicating greater overall mood disturbance. For side effects, data displayed reflect the percentage of the sample to report the respective item.

**Mood and Sleepiness**

Table 3 shows the means and standard deviations for each time point on the POMS-SF and KSS. Analysis the POMS-SF subscales revealed a significant main
effect of Drug Condition for the Vigour-Activity subscale, $F(1, 17)=8.86, p=.008$, $\eta_p^2=.343$. This effect was subsumed by a significant Drug Condition x Time interaction, $F(1, 17)=15.68, p=.001$, $\eta_p^2=.480$, indicating that for the placebo condition, there was a significant reduction in scores from pre-ingestion to post-ingestion ($p<.001, g=.99$), with no significant differences in the modafinil condition ($p=.325, g=.21$). A significant main effect of Time was found for the Fatigue-Inertia subscale, $F(1, 17)=16.61, p=.001$, $\eta_p^2=.494$. Again, this effect was encompassed within a significant Drug Condition x Time interaction, $F(1, 17)=4.90, p=.041$, $\eta_p^2=.224$, indicating that for the placebo condition, there was a significant increase in scores from pre-ingestion to post-ingestion ($p<.001, g=1.23$), with no significant difference in the modafinil condition ($p=.184, g=.45$). A significant Drug Condition x Time interaction was also observed for the Depression-Dejection subscale, $F(1, 17)=4.83, p=.042$, $\eta_p^2=.221$, indicating that for the modafinil condition, there was a significant reduction in scores from pre-ingestion to post-ingestion ($p=.015, g=.88$), with no significant differences from pre-ingestion to post-ingestion in the placebo condition ($p=.933, g=.02$). No other significant main effects or interactions were found for any of the other POMS-SF subscales ($p>.05$).

Analysis of the KSS revealed a significant main effect of Drug Condition, $F(1, 17)=12.78, p=.002$, $\eta_p^2=.429$, and a non-significant main effect of Time, $F(1, 17)=2.70, p=.188$, $\eta_p^2=.137$. These effects were however qualified within a significant Drug Condition x Time interaction, $F(1, 17)=9.57, p=.007$, $\eta_p^2=.360$, revealing a significant increase in sleepiness for the placebo condition from pre-ingestion to post-ingestion ($p=.001, g=1.07$), with no significant changes in sleepiness from pre-ingestion to post-ingestion for the modafinil condition ($p=.859, g=.34$).
Table 3

Means (and Standard Deviations) for the POMS-SF Subscales and KSS at Pre-Ingestion and Post-Ingestion

<table>
<thead>
<tr>
<th>POMS-SF subscales</th>
<th>Modafinil Pre-ingestion</th>
<th>Placebo Pre-ingestion</th>
<th>Modafinil Post-ingestion</th>
<th>Placebo Post-ingestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension-Anxiety</td>
<td>3.00 (3.46)</td>
<td>2.89 (3.60)</td>
<td>3.72 (5.07)</td>
<td>2.00 (2.95)</td>
</tr>
<tr>
<td>Depression-Dejection</td>
<td>1.33 (2.09)</td>
<td>1.22 (2.21)</td>
<td>.00 (.00)</td>
<td>1.28 (3.27)</td>
</tr>
<tr>
<td>Anger-Hostility</td>
<td>.28 (1.18)</td>
<td>.33 (.69)</td>
<td>.06 (.24)</td>
<td>.28 (1.00)</td>
</tr>
<tr>
<td>Vigour-Activity</td>
<td>8.50 (5.92)</td>
<td>8.61 (4.59)</td>
<td>9.83 (6.21)</td>
<td>4.44 (3.62)</td>
</tr>
<tr>
<td>Fatigue-Inertia</td>
<td>2.83 (2.81)</td>
<td>1.94 (2.01)</td>
<td>4.28 (3.37)</td>
<td>6.44 (4.63)</td>
</tr>
<tr>
<td>Confusion-Bewilderment</td>
<td>1.78 (2.16)</td>
<td>2.06 (3.08)</td>
<td>1.83 (2.92)</td>
<td>2.33 (3.12)</td>
</tr>
<tr>
<td>Sleepiness (KSS)</td>
<td>4.72 (1.02)</td>
<td>4.67 (1.24)</td>
<td>4.22 (1.73)</td>
<td>6.11 (1.41)</td>
</tr>
</tbody>
</table>

Note: Score ranges for POMS-SF subscales are: Tension-Anxiety ranges 0-24, Depression Dejection ranges 0-32, Anger-Hostility ranges 0-28, Vigour-Activity ranges 0-24, Fatigue Inertia ranges 0-20, and Confusion-Bewilderment ranges 0-20. For each subscale, higher scores indicate greater levels of specified mood. For the KSS, higher scores indicate greater levels of sleepiness.

Alertness

Descriptive statistics for the VAS of Subjective Performance and VAS of Subjective Drug Effects are displayed in Table 4. Analysis of the VAS of Subjective Performance revealed significant main effects of Time on the ‘I do not feel that my driving would be impaired right now’ item, $F(1,17)=13.00$, $p=.002$, $\eta^2=.433$, with a significant increase at pre-ingestion ($M=1.46$, $SD=2.08$) relative to post-ingestion.
(M=3.39, SD=2.41), and the ‘I feel capable of driving safely right now’ item, $F(1,17)=17.03$, $p=.001$, $\eta_p^2=.500$, with a significant increase at pre-ingestion (M=1.04, SD=2.04) relative to post-ingestion (M=2.71, SD=2.46). A significant main effect of Drug Condition was found on the ‘I feel alert’ item, $F(1,17)=11.10$, $p=.004$, $\eta_p^2=.395$, which was subsumed by a significant Drug Condition x Time interaction, $F(1,17)=7.94$, $p=.012$, $\eta_p^2=.318$. This interaction indicated that while there were no significant differences between pre-ingestion and post-ingestion for the modafinil condition ($p=.189$, $g=.42$), there was a significant decrease for the placebo condition ($p=.034$, $g=.72$) that did not maintain significance following a Bonferroni correction ($\alpha=.025$). On the ‘I feel that I will be able to perform the attention tasks to the best of my ability’ item, there were main effects of Drug Condition, $F(1,17)=7.56$, $p=.014$, $\eta_p^2=.308$, Time, $F(1,17)=23.26$, $p<.001$, $\eta_p^2=.577$, and a significant Drug x Time interaction, $F(1,17)=8.71$, $p=.009$, $\eta_p^2=.339$, by which there was a significant decrease in agreement from pre-ingestion to post-ingestion for the placebo ($p<.001$, $g=1.34$), but not the modafinil condition ($p=.307$, $g=.27$). No other significant main effects or interactions were found on the VAS of Subjective Performance ($p>.05$).

Analysis of the VAS of Subjective Drug Effects revealed a significant main effect on the ‘Strength of drug effect’ item, with significantly greater strength indicated in the modafinil relative to placebo condition, $t(17)=2.15$, $p=.046$, $g=.60$. A significant main effect was also found for the ‘Liking of drug effect item’ with significantly greater ratings in the modafinil relative to placebo condition, $t(17)=2.75$, $p=.012$, $g=.82$. Consistent with the VAS of Subjective Performance, a significant main effect was also observed for the ‘Alert level’ item with greater alertness indicated by the modafinil relative to placebo condition, $t(17)=3.19$, $p=.003$, $g=.88$. No other significant main effects or interactions were found on the VAS of Subjective Drug Effects ($p>.05$).
\[ p = .005, g = .83 \]. No significant differences were observed for the ‘Intoxication’ item,
\[ t(17) = .63, p = .538, g = .18 \].

Table 4

*Means (and Standard Deviations) for the VAS of Subjective Performance at Pre-Ingestion and Post-Ingestion, and VAS of Subjective Drug Effects at Post-Ingestion*

<table>
<thead>
<tr>
<th></th>
<th>Modafinil Pre-ingestion</th>
<th>Modafinil Post-ingestion</th>
<th>Placebo Pre-ingestion</th>
<th>Placebo Post-ingestion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAS of Subjective</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel alert</td>
<td>3.63 (1.09)</td>
<td>2.89 (2.16)</td>
<td>3.73 (1.45)</td>
<td>5.08 (2.15)</td>
</tr>
<tr>
<td>Ability for attention tasks</td>
<td>2.34 (1.26)</td>
<td>2.84 (2.24)</td>
<td>2.58 (1.16)</td>
<td>4.84 (2.03)</td>
</tr>
<tr>
<td>Unimpaired driving</td>
<td>1.47 (2.38)</td>
<td>2.97 (2.56)</td>
<td>1.45 (2.12)</td>
<td>3.81 (3.04)</td>
</tr>
<tr>
<td>Capable of driving safe</td>
<td>.96 (1.89)</td>
<td>2.63 (2.86)</td>
<td>1.12 (2.60)</td>
<td>2.81 (2.92)</td>
</tr>
<tr>
<td><strong>VAS of Subjective Drug</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength of drug effect</td>
<td>3.63 (2.95)</td>
<td></td>
<td>2.04 (2.17)</td>
<td></td>
</tr>
<tr>
<td>Liking of the drug effect</td>
<td>5.75 (2.06)</td>
<td></td>
<td>4.05 (1.05)</td>
<td></td>
</tr>
<tr>
<td>Alert level</td>
<td>5.99 (2.65)</td>
<td></td>
<td>3.94 (2.12)</td>
<td></td>
</tr>
<tr>
<td>Intoxication</td>
<td>1.27 (1.91)</td>
<td></td>
<td>.92 (1.79)</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Scores range from 0 – 10. For the VAS of Subjective Performance, lower scores indicate more agreement with the item. For the VAS of Subjective Drug Effects, higher scores indicate a greater degree of the item (e.g. higher score equals stronger drug effect).*
Reaction Time

Table 5 shows the mean RTs between Drug Condition for each of the ‘go’ trials in the Flanker Go/Nogo task. Analysis of RT (ms) revealed a significant main effect of Congruency, $F(1,17)=63.28$, $p<.001$, $\eta_p^2=.788$, with significantly slower RTs for incongruent stimuli ($M=485$, $SD=44$) relative to congruent stimuli ($M=454$, $SD=46$). There was also a significant main effect of Time, $F(1,17)=6.67$, $p=.016$, $\eta_p^2=.282$, with participants demonstrating significantly faster RTs at post-ingestion ($M=459$, $SD=41$) compared to pre-ingestion ($M=480$, $SD=53$). A non-significant main effect was observed for Drug Condition, $F(1,17)=.08$, $p=.930$, $\eta_p^2<.001$, indicating there were no overall differences in RT between the modafinil ($M=470$, $SD=49$) and placebo conditions ($M=469$, $SD=50$). A trend towards significance was however observed for the Drug Condition x Time interaction, $F(1,17)=4.27$, $p=.054$, $\eta_p^2=.202$, and due to its near significance and large size of effect, Bonferroni corrected tests of simple main effects were conducted. Displayed in Figure 1, pairwise comparisons revealed a significant decrease in RT from pre-ingestion to post-ingestion for the modafinil condition ($p=.016$, $g=.56$), with no significant differences between pre-ingestion and post-ingestion in the placebo condition ($p=.170$, $g=.18$).

The Drug Condition x Congruency interaction, $F(1,17)=.18$, $p=.676$, $\eta_p^2=.011$, the Time x Congruency interaction, $F(1,17)=2.27$, $p=.150$, $\eta_p^2=.118$, and the hypothesised three way Drug Condition x Time x Congruency interaction, $F(1,17)=.26$, $p=.616$, $\eta_p^2=.015$, were all non-significant.
Table 5

Means (Standard Deviations) and 95% CIs for Reaction Time (ms) at Pre-Ingestion and Post-Ingestion

<table>
<thead>
<tr>
<th></th>
<th>Modafinil</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M$ ($SD$)</td>
<td>95% CI</td>
<td>$M$ ($SD$)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Pre-ingestion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go Congruent</td>
<td>468 (66)</td>
<td>[435, 501]</td>
<td>458 (60)</td>
<td>[428, 488]</td>
</tr>
<tr>
<td>Go Incongruent</td>
<td>503 (68)</td>
<td>[470, 537]</td>
<td>490 (54)</td>
<td>[463, 516]</td>
</tr>
<tr>
<td>Post-ingestion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go Congruent</td>
<td>440 (42)</td>
<td>[420, 461]</td>
<td>451 (50)</td>
<td>[426, 475]</td>
</tr>
<tr>
<td>Go Incongruent</td>
<td>468 (42)</td>
<td>[447, 489]</td>
<td>478 (50)</td>
<td>[453, 503]</td>
</tr>
</tbody>
</table>

Figure 1. Mean reaction times (ms) for modafinil and placebo conditions at pre-ingestion and post-ingestion time points (error bars indicate 95% CIs)
Accuracy

Descriptive statistics for accuracy (% of correct responses) for each condition are displayed in Table 6. Analysis of accuracy showed a significant main effect of Trial Type, $F(1,17)=25.35, p<.001, \eta^2_p=.599$, whereby greater accuracy was observed for nogo trials ($M=98.08, SD=1.65$) relative to go trials ($M=94.75, SD=2.93$). A significant main effect of Congruency, $F(1,17)=8.24, p=.011, \eta^2_p=.326$, indicated lower accuracy for incongruent stimuli ($M=95.91, SD=2.27$) relative to congruent stimuli ($M=96.92, SD=1.85$). The main effect of Time was non-significant, $F(1,17)=.25, p=.624, \eta^2_p=.014$, as was the main effect of Drug Condition, $F(1,17)=.01, p=.950, \eta^2_p<.001$. No significant interactions were observed for Drug Condition x Congruency, $F(1,17)=.01, p=.916, \eta^2_p=.001$, Drug Condition x Trial Type, $F(1,17)=3.50, p=.079, \eta^2_p=.171$, or Drug Condition x Time, $F(1,17)=1.93, p=.183, \eta^2_p=.102$. The three way Drug Condition x Congruency x Time interaction was also non-significant, $F(1,17)=.02, p=.885, \eta^2_p=.001$. No other significant main effects or interactions were found ($p>.05$).
Table 6

*Means (Standard Deviations) and 95% CIs for Accuracy (% of correct responses) at Pre-Ingestion and Post-Ingestion*

<table>
<thead>
<tr>
<th></th>
<th>Modafinil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Pre-ingestion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go Congruent</td>
<td>94.31 (5.06)</td>
<td>[91.79, 96.82]</td>
</tr>
<tr>
<td>NoGo Congruent</td>
<td>98.47 (2.12)</td>
<td>[97.42, 99.53]</td>
</tr>
<tr>
<td>Go Incongruent</td>
<td>94.31 (3.72)</td>
<td>[92.46, 96.16]</td>
</tr>
<tr>
<td>NoGo Incongruent</td>
<td>98.06 (2.91)</td>
<td>[96.61, 99.51]</td>
</tr>
<tr>
<td><strong>Post-ingestion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go Congruent</td>
<td>94.94 (5.00)</td>
<td>[92.46, 97.42]</td>
</tr>
<tr>
<td>NoGo Congruent</td>
<td>99.83 (.38)</td>
<td>[99.64, 100.02]</td>
</tr>
<tr>
<td>Go Incongruent</td>
<td>94.17 (4.59)</td>
<td>[91.88, 96.45]</td>
</tr>
<tr>
<td>NoGo Incongruent</td>
<td>97.06 (3.00)</td>
<td>[95.56, 98.55]</td>
</tr>
</tbody>
</table>
**N2 Amplitude**

Figures 2 and 3 show the grand mean averaged waveforms at the frontal site Fz for modafinil and placebo conditions, respectively, peaking at approximately 310ms post-stimulus onset. Visual inspection clearly demonstrates the effect of Trial Type and Congruency on the N2 component, with evidently greater N2 amplitude for no-go trials and trials with incongruent stimuli. No apparent distinctions between the modafinil and placebo condition are evident from the Figures.

*Figure 2.* Grand mean waveforms for the modafinil condition at the midline frontal site (Fz)
Figure 3. Grand mean waveforms for the placebo condition at the midline frontal site (Fz)

Table 7 shows the peak N2 amplitude (µV) following each of the Flanker Go/Nogo trials. The main effect of Congruency was significant, $F(1,17)=27.72$, $p<.001$, $\eta^2=.620$, indicating that overall N2 amplitude was significantly greater in response to incongruent stimuli ($M=-2.03$, $SD=2.78$) relative to congruent stimuli ($M=-.78$, $SD=2.88$). There was also a significant main effect of Trial Type, $F(1,17)=18.77$, $p<.001$, $\eta^2=.525$, such that N2 amplitude was significantly greater following nogo trials ($M=-2.12$, $SD=2.72$) compared to go trials ($M=-.69$, $SD=3.02$). The Trial Type x Congruency interaction approached significance, $F(1,17)=3.92$, $p=.064$, $\eta^2=.187$, and Bonferroni corrected tests of simple main effects revealed significantly greater difference in N2 amplitude between go trials ($M=-.97$, $SD=2.99$) and nogo trials ($M=-3.09$, $SD=2.87$) for incongruent stimuli ($p<.001$, $g=.71$), relative to the difference in N2 amplitude between go trials ($M=-.40$, $SD=3.29$) and nogo trials ($M=-1.16$, $SD=2.87$) for congruent stimuli ($p=.165$, $g=.24$).
The main effect for Drug Condition was non-significant, $F(1,17)=.40$, $p=.536$, $\eta^2_p=.023$, suggesting that overall N2 amplitude did not differ between the modafinil ($M=-1.29, SD=2.63$) and placebo conditions ($M=-1.52, SD=3.13$). No significant interactions were found for Drug Condition x Trial Type, $F(1,17)=.01$, $p=.923$, $\eta^2_p=.001$, or for Drug Condition x Congruency, $F(1,17)=.024$, $p=.879$, $\eta^2_p=.001$. The three way Drug Condition x Trial Type x Congruency interaction was non-significant, $F(1,17)=1.85$, $p=.192$, $\eta^2_p=.098$.

Table 7

Means (Standard Deviations) and 95% CIs for N2 Amplitude (µV)

<table>
<thead>
<tr>
<th></th>
<th>Modafinil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M$ ($SD$)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Go Congruent</td>
<td>-.38 (3.40)</td>
<td>[-2.08, 1.31]</td>
</tr>
<tr>
<td>NoGo Congruent</td>
<td>-.91 (2.82)</td>
<td>[-2.32, .49]</td>
</tr>
<tr>
<td>Go Incongruent</td>
<td>-.74 (2.86)</td>
<td>[-2.16, .68]</td>
</tr>
<tr>
<td>NoGo Incongruent</td>
<td>-3.12 (2.71)</td>
<td>[-4.47, -1.78]</td>
</tr>
</tbody>
</table>

Discussion

The aim of the present study was to investigate the effect of 200mg of modafinil on both behavioural and ERP correlates of inhibitory control, in a sample of healthy, non-sleep deprived individuals. Participants were compared on RT, accuracy and N2 amplitude across two experimental conditions. The hypothesis that the increase in RT from congruent trials to incongruent trials would be significantly reduced for the modafinil condition at post-ingestion testing compared to the placebo
condition was not supported, as indicated by the non-significant Drug Condition x Time x Congruency interaction. While a main effect of Congruency suggests participants did have slower RTs for incongruent stimuli relative to congruent stimuli, this did not significantly vary as an effect of Drug Condition. A trend towards a significant Drug Condition x Time interaction for RT was however observed, with significant reductions in RT from pre-ingestion to post-ingestion found for the modafinil and not the placebo condition. Nevertheless, this was observed for both congruent and incongruent trials of the task, suggesting that the effect was independent from inhibitory control processes.

The second hypothesis, that the decrease in accuracy from congruent trials to incongruent trials would be significantly reduced for the modafinil condition at post-ingestion compared to the placebo condition, was also not supported. Again, this is evident given the non-significant Drug Condition x Time x Congruency interaction. A main effect of Congruency was found, indicating there were significantly less accurate responses to incongruent stimuli relative to congruent stimuli, though again this was not affected by Drug Condition.

A similar pattern was also observed for amplitude of the N2 component. The hypothesis that the combined nogo and flanker effect of the Flanker Go/Nogo task would result in significantly increased N2 amplitude in modafinil conditions relative to placebo conditions was not supported, as evidenced by the non-significant Drug Condition x Trial Type x Congruency interaction. While significant main effects were observed for Trial Type and Congruency, with a trend towards a significant Trial Type x Congruency interaction; there was no interaction of Drug Condition with either of these variables.
Mood, Fatigue and Alertness

Significant Drug Condition x Time interactions were observed on both Vigour-Activity and Fatigue-Inertia subscales of the POMS-SF. Interestingly, these interactions were not a product of significant enhancement in the modafinil condition, but rather the result of significantly lower ratings in the placebo condition. Modafinil did however appear to improve ratings on the Depression-Dejection subscale in comparison to placebo, though it is worth noting that ratings on the Depression-Dejection subscale were generally low, with scores of 0 frequently observed at baseline for both conditions. The lack of significant differences on any other subscale suggests that modafinil had little influence on subjective mood as measured by the POMS-SF. These findings are concordant with previous literature, whereby modafinil is rarely associated with negative changes in subjective mood, though in some cases has been found to improve mood related to alertness and energy (Battleday & Brem, 2015; Minzenberg & Carter, 2008; Repantis et al., 2010). Also consistent with past literature; reported side effects were minor and non-distressing, and usually observed in both modafinil and placebo conditions. Confidence of ingesting modafinil was found to be significantly greater in the modafinil condition relative to placebo. Despite this, median scores for both conditions were still at chance (≤50%), with large variation across participants, suggesting effects of modafinil were mostly subtle and not readily detected.

The effects observed on the KSS were consistent with those found on the Fatigue-Inertia subscale of the POMS-SF, with a significant increase in sleepiness reported from pre-ingestion to post-ingestion for the placebo condition, compared to non-significant decreases in sleepiness for the modafinil condition. Alertness items on VAS measures indicate there were significant decreases in alertness from pre-
post-ingestion in the placebo condition, with no significant changes to alertness for
the modafinil condition.

Considered together, results of the POMS-SF, KSS and VAS suggest that participants’ subjective wakefulness and alertness significantly decreased throughout the session, though that this fatigue was mitigated by modafinil. Rather than providing any significant enhancement of alertness or wakefulness above baseline, modafinil instead provided an effect of maintenance within what was evidently a fatigue-inducing environment for participants. These findings are consistent with the role of modafinil as a wake-promoting agent, and with the effects often observed in studies involving sleep-deprivation (Repantis et al., 2010).

It is not clear why the present study induced fatigue to such an extent, given that the sample comprised healthy, well-rested individuals. It is possible that this is a common effect of many studies investigating effects of modafinil in healthy populations, as experimental sessions are often long and tedious due to accounting for peak plasma levels (Minzenberg & Carter, 2008). Many studies in non-sleep deprived populations do not examine within-session fatigue, therefore the notion that participants on modafinil may simply be more awake than placebo controls by the time testing occurs is an important confound to consider. It is also possible that, being an ERP study, the present study exacerbated within-session fatigue beyond what would normally be observed, given that participants were required to remain still in a dimly lit room during cognitive testing. Post-ingestion measures of the POMS-SF, KSS and VAS were taken at approximately 3.25 hours post-ingestion, directly following cognitive testing. Increased sleepiness in the placebo condition may have therefore been a result having completed the measures directly after
testing, and consequently may not have been an accurate index of fatigue and alertness prior to performing the tasks.

**Behavioural and ERP Correlates of Inhibitory Control**

In relation to the behavioural hypotheses, the present results provided little support for effects of modafinil in the selective improvement of inhibitory control processes. Incongruent stimuli were associated with the slower RTs and less accurate responses overall, suggesting that the task was effective at eliciting a flanker effect. This finding was in accord with the precursory behavioural hypotheses, as well as previous literature advocating the use of the Flanker Go/NoGo paradigm for the measurement of inhibitory processes (Heil et al., 2000). However, the flanker effect did not significantly vary between the modafinil and placebo conditions, suggesting that modafinil did not enhance the extent to which participants were able to effectively respond to inhibitory control-related stimuli. Further, although overall reductions in RT were found for the modafinil condition from pre- to post-ingestion, this effect did not appear to be driven by an enhancement of inhibitory control, due to the lack of interaction with Congruency. Non-significant effects of Time or Drug Condition in the accuracy data do however suggest little evidence for a speed / accuracy trade-off for the effects on RT.

These findings are in contrast to those previously reported by Turner et al. (2003), whereby significantly reduced error rates and stop-signal RTs were observed in participants following modafinil administration. Rather, the present results are more closely aligned with the findings reported in studies by Randall et al. (2004) and Randall, et al. (2005b), in which modafinil only enhanced performance on congruent trials of the Stroop task, and not the inhibitory control-related incongruent trials. This interaction also reflects the behavioural findings reported by Minzenberg
et al. (2014), whereby significant decreases in RT for both congruent and incongruent trials of the POP task were found between testing blocks for the modafinil condition, but not the placebo condition.

Within previous literature investigating effects of modafinil on healthy individuals, a number of studies have failed to detect differences on behavioural measures of inhibitory control, but have reported differences in neural activity associated with inhibitory control processes (Minzenberg et al., 2014; Minzenberg et al., 2008; Rasetti et al., 2010). This has been suggested to be due to the insufficient sensitivity of tasks to detect enhancement in healthy populations, often as a result of ceiling effects (Battleday & Brem, 2015). The use of electrophysiological and neuroimaging techniques may therefore provide additional insight regarding the true extent of effects, even when no differences on behavioural measures are observed.

The electrophysiological results of the present study, however, were supportive of the findings of the behavioural data, with no apparent effects of modafinil on inhibitory control-related processes. Amplitude of the N2 component was shown to be significantly greater for incongruent stimuli relative to congruent stimuli, and for nogo trials relative to go trials, and the increase in N2 amplitude from go trials to nogo trials was significantly greater for incongruent stimuli relative to congruent stimuli, as was proposed by the original hypothesis. This increase in amplitude was not found to be greater for the modafinil condition relative to the placebo condition, suggesting that the extent of inhibitory control resources did not differ between the conditions.

Considered together, the results of the present study provide little support for the notion that modafinil may selectively enhance inhibitory control processes. The overall pre- to post-ingestion reduction in RT for the modafinil condition is however
similar to effects previously observed in past studies (Minzenberg et al., 2014; Randall et al., 2004; Randall, et al., 2005b). Although it provides no evidence for the selective enhancement of inhibitory control, a reduction of RT may provide some tentative evidence for a general enhancement of processing speed following modafinil ingestion, possibly through the enhancement of sustained attention and vigilance. Past research has indicated improvements on these processes following modafinil administration, with greater performance observed on the RVIP task of sustained attention (Randall, Shneerson & File, 2005a; Randall et al., 2005b), and Detection of Repeated Numbers (DRN) vigilance task (Baranski, Pigeau, Dinich, & Jacobs, 2004). Despite this, evidence in this area remains equivocal, and is beyond both the aims and scope of the present study to attribute effects with any certainty. The present results do however provide grounds for future investigation in this area, and particularly research utilising ERP techniques. Investigation of early ERP components in relation to performance on tasks of sustained attention may provide more conclusive evidence regarding effects on early processing and processing speed.

It is, however, worth considering the apparent confound of within-session fatigue when regarding effects of enhanced performance. The results of the analyses conducted on the POMS-SF, KSS and VAS indicated that participants in the placebo condition experienced significant increases in sleepiness and decreases in alertness throughout the session, with no apparent effect in the modafinil condition, likely due to the wake-promoting effects of the drug. Differences in subjective wakefulness and alertness between the conditions may therefore in itself have causative influence over differences in behavioural performance, irrespective of any selective
neuroenhancement to specific cognitive processes (Randall, Shneerson & File, 2005a).

This is a problematic notion for past research investigating effects of modafinil, or any proposed cognitive enhancer, given that indices of wakefulness and within-session fatigue are often overlooked when samples comprise healthy, non-sleep deprived individuals (Randall, Shneerson, & File, 2005a). The study by Turner et al. (2003) is one few to report clear effects of behavioural enhancement on inhibition-related paradigms, however no ratings of sleepiness or fatigue were taken throughout the sessions, and therefore the extent to which this may have influenced the results is not evident. By contrast, in studies where wakefulness and alertness are monitored throughout the session, few effects of modafinil are observed when indices of fatigue do not vary between groups (Randall et al., 2004; Randall, et al., 2005b). The notion that within-session fatigue may account for the inconsistencies in the literature is important to consider, and is a limitation of existing reviews that have failed to appropriately address this issue (Battleday & Brem, 2015). Again, it is possible that effects of fatigue in the present study were exacerbated beyond what is normally observed in the literature due to the nature of the present design, therefore future studies utilising ERP techniques should be particularly conscious of this potential confound.

**Methodological Limitations**

Similar to previous studies utilising simple test paradigms of cognitive performance (Minzenberg & Carter, 2008; Rasetti et al., 2010); an additional limitation of the present study is the substantial ceiling effects observed in the Flanker Go/Nogo paradigm. This was particularly apparent for the accuracy data, whereby participants were performing near ceiling across all time points of the study,
irrespective of Drug Condition. Despite this, large effects of Congruency and Trial Type were still discernible within the data, though it could be argued that ceiling performance may have masked what would have been more subtle effects of modafinil on performance.

In their review, Battleday and Brem (2015) argued that ceiling effects in low-complexity tasks are a primary factor as to why inconsistencies in results are often observed across studies. Considering the recommendation to use novel and more complex tasks to assess neuroenhancement, the present study compromised; utilising a well validated measure of a specific cognitive process, and attempting to increase task difficulty through brief stimulus presentations and greater levels of visual and phonological interference. Although it is possible that effects of modafinil on inhibitory control may have been observed had the task been more difficult, it is worth noting that modafinil did not seem to interact with inhibitory processes within the reaction time data or the electrophysiological data of the N2 component, both of which are less susceptible to ceiling effects. This is nonetheless something to be explored further in future research, as effective increases in task difficulty or cognitive load may potentially manifest effects of modafinil not found by the present study.

Also similar to previous research (Minzenberg & Carter, 2008; Minzenberg et al., 2014), practice effects both within- and between-sessions represent a considerable limitation of the study. Irrespective of Drug Condition, significant decreases in RT were noted from pre- to post-ingestion, and preliminary analyses including order of drug administration revealed decreases from session 1 to session 2. In these analyses, there were no interactions between order and the interactions of interest and therefore, order was omitted from subsequent analyses given power and
sample size limitations. It is possible however that these effects could be better investigated using a more powerful design or a Mixed Models approach to analysis. Despite this, effects of Drug Condition were still discernible in relation to Time, where although practice effects were evident in both conditions, significant reductions in RT were observed only following modafinil ingestion. Further, the electrophysiological results were still in accord with overall results of RT, though future research may also wish to consider collecting ERP data at baseline, as this was beyond the means of the present study.

It may be argued that had the present study used a between-subjects design, effects of modafinil would have been more readily observable, though this is not necessarily true of the current literature, with mixed results observed in both parallel and crossover designs. Nonetheless, while it was not viable for the present study to use a between-subjects design due to limits on time and sampling, future studies may wish to consider doing so in order to avoid effects of practice on susceptible tasks.

**Summary and Conclusions**

The present study aimed to investigate the extent to which 200mg of modafinil may influence behavioural and electrophysiological correlates of inhibitory control, within a sample of healthy, non-sleep deprived individuals. Expanding on previous research examining effects using only behavioural measures of performance, the present study utilised a temporally-precise, ERP technique as an additional measure of inhibitory control. In sum, the results of the present study validated the role of modafinil as a wakefulness and alertness promoting agent, though provided no evidence for its use in the selective enhancement of inhibitory control-related processes. Some tentative evidence is provided for the enhancement in processing speed via effects on vigilance, though further research is necessary to
clarify these effects. Important considerations are however raised regarding the effect of within-session fatigue in studies attempting to identify effects of neuroenhancement, given the long experimental sessions that are often necessary, and potential for induced fatigue.

In terms of the efficacy of modafinil as a cognitive enhancing agent, the results of the present study provide little evidence beyond effects on processing speed. Equivocal evidence remains for effects on other executive functions, as well as processes of attention, learning and motivation (Battleday & Brem, 2015; Repantis et al., 2010). The extent to which these effects are observed in the absence of experimental fatigue is, however, a consideration requiring more attention in future studies and reviews.
References


prevalences and trends in non-specific psychological distress. *Psychological Medicine, 32*(6), 959-976. doi:10.1017/s0033291702006074


Appendix A

INFORMATION SHEET

The Effect of Modafinil on Cognitive Processes and Brain Activity

Chief Investigators: Dr Raimondo Bruno & Dr Allison Matthews
Researchers: Caitlin Harris & Oliver De Angelis *

*This research is being conducted as part of an Honours degree in the School of Psychology, UTAS.

We would like to invite you to participate in a study aiming to better understand the way that the prescription drug Modafinil effects cognitive processes such as attention and associated brain activity. The use of this drug is increasing Australia wide, and we are interested in better understanding its effects. There have been a number of studies which have shown some effects of stimulant drugs on cognitive processes but very few studies have examined Modafinil. Getting a better understanding about Modafinil is particularly important, not just to understand how the drug affects cognition, but also to be able to provide information for doctors to give to potential users of the drug.

Why have I been invited to participate in this research?
You are invited to take part in the study if you are male and aged 18-30 years old. In order for the results of the study to be clear, all participants need to speak English fluently, and have had no previous neurological or mental health problems. In addition, participants must NOT use illicit drugs, smoke cigarettes daily, consume alcohol at harmful levels or be female.

What will my participation involve?
Participating in this study is unlikely to cause any discomfort or distress. Firstly, if you are interested in taking part in the study, you will be invited to complete a series of confidential screening questionnaires. These will enquire about what your mood has been like recently. This will include a psychological distress scale, schizotypal personality questionnaire, a psychosis screener and some questions regarding your alcohol, caffeine and drug use. All data collected will be kept in the strictest confidence, and the way we maintain this is described below. This screening process is simply to ensure that participants in the study are not taking medications or experiencing other issues that may cause a negative response to Modafinil.

During the study, we will ask for some basic information about yourself (such as age, sex, years of schooling). During each testing session, you will be fitted with an electrode cap for measuring your brain activity. You will be asked to complete some computer-based tasks which relate to cognitive processes such as attention. In these
tasks you will respond with a button press when particular stimuli appear on the screen. Previous studies using the same dose of Modafinil have found side effects for some participants, including dry mouth, mild headaches and mild nausea. There will be two testing sessions which will occur at the University of Tasmania, and will take around four hours each. You will be reimbursed up to $80 for your time and out-of-pocket expenses.

Before taking part in the study you must organise for a reliable friend or family member to collect you from the lab at the end of the testing session, in case you are still experiencing any effects following the possible administration of Modafinil. The researcher will check that this has been organised before the testing session begins. When the nominated person collects you, they will be given a copy of the medication information sheet about Modafinil, and the main points will be verbally explained. Namely, it will be explained that they should ensure you do not drive a vehicle or operate machinery for the rest of the day, and do not consume alcohol. In the unlikely event that you do experience unpleasant side effects while completing the testing, the researchers are trained in first aid, and the chief investigators will be available on site to provide further assistance if required. Additionally, the researcher will explain that in the unlikely event of you experiencing an adverse reaction once you have left the premises, you should contact your doctor or be taken to hospital immediately.

There are no specific risks associated with the measurement of brain activity. However, if you have sensitive skin there is a small possibility of a slight skin reaction from electrode preparation materials. If you believe there is a chance that your skin may react you are advised to reconsider participation.

**How private is the information that I give?**

It is important for you to know that all data collected will be kept in the strictest confidence. All data will be identified by a coding system and no names or contact numbers will appear on any records. In this way, your identity is protected, and there will be no risk of legal or social problems arising from your participating in the study. All information gathered in the study will be reported as grouped data, and because no personal information is recorded, no individual participants will be identifiable in the research output. Data from the study will be stored securely for five years in locked cabinets in the School of Psychology, as is legally required, and then destroyed by shredding.

**Can I withdraw from the research if I wish?**

Participation in this study is entirely voluntary. You may, at any time, decline to answer any question you so wish, or withdraw from the study without effect or explanation.
You will be given a copy of this information sheet to keep. Please retain this information sheet in case you decide at a later date that you would like to retract your data from the study.

**Who do I need to contact if I have any questions about the research?**
If you would like more information about the research, please contact Dr Allison Matthews on 62267236 (or email Allison.Matthews@utas.edu.au) or Dr Raimondo Bruno 6226 2190 (Raimondo.Bruno@utas.edu.au). If you would like to find out about the results of the study, these will be available from Dr Matthews after November 2016.

**Has this research been approved by an ethics committee?**
This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. Please quote the ethics reference number H0011386.

**Who can I contact if I have any concerns?**
If you have any personal concerns related to the study, you may choose to discuss these concerns confidentially with a counsellor at the University Psychology Clinic free of charge. Confidential appointments may be made on (03) 6226 2805.

Thank you for your interest in the study and for taking the time to read this information sheet. We hope you will be interested in participating in this study.

Raimondo Bruno & Allison Matthews Oliver De Angelis/Caitlin Harris
Chief Investigators Student Researchers
(03) 6226 2190 or (03) 6226 7236
CONSENT FORM
The Effect of Modafinil on Cognitive Processes and Brain Activity

1. I have read and understood the 'Information Sheet' for this study.
2. I have read and understood the ‘Consumer Medicine Information’ regarding modafinil.
3. The nature and possible effects of the study have been explained to me.
4. I understand that the study involves:
   - Attending two testing sessions of approximately four hours duration
   - Completing a series of cognitive tasks while my brain activity is measured
5. I understand that all research data will be securely stored on the University of Tasmania premises for five years, and will then be destroyed.
6. Any questions that I have asked have been answered to my satisfaction.
7. I agree that research data gathered from me for the study may be published provided that I cannot be identified as a participant.
8. I understand that the researchers will maintain my identity confidential and that any information I supply to the researcher(s) will be used only for the purposes of the research.
9. I agree to participate in this investigation and understand that I may withdraw at any time without any effect, and if I so wish, may request that any data I have supplied to date be withdrawn from the research.
10. This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. Please quote the ethics reference number H0011386.

_________________________
Name of Participant:

_________________________
Signature: Date:

Statement by Investigator

☐ I have explained the project & the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation

_________________________
Name of investigator

_________________________
Signature of investigator Date
Appendix B

Ethics Approval Letter

-----Original Message-----

From: Lauren Black@utas.edu.au [mailto:Lauren.Black@utas.edu.au]
Sent: Wednesday, 30 March 2016 1:22 PM
To: Raimondo Bruno
Cc: chris.wake@utas.tas.gov.au, Allison Matthews, Jessica Hartley, Lauren Black
Subject: Notification of Amendment Approval: H0011386 The effect of modafinil on simulated driving performance

Dear AssocProf Bruno

Ethics Ref: H0011386
Title: The effect of modafinil on simulated driving performance

This email is to confirm that the following amendment was approved by the Chair of the Tasmania Health and Medical Human Research Ethics Committee on 24/3/2016:

Measurement of brain activity (EEG) during the experimental tasks Changes to the experimental tasks Omission of the baseline testing condition Registered nurse is no longer on site MODAFINIL info and consent forms_revised2016

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the National Statement on Ethical Conduct in Human Research (NHMRC 2007).

This email constitutes official approval. If your circumstances require a formal letter of amendment approval, please let us know.

Should you have any queries please do not hesitate to contact me.

Kind regards

Lauren Black

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Lauren Black
Executive Officer - Ethics
Office of Research Services
University of Tasmania
Appendix C

Experimental session questionnaire

Date ____/____/____
Participant ID ___________

1. Check that participant has abstained from alcohol for 24 hours and illicit drug use since completing the screening questionnaire

2. Weight ___________ kg
   Height ___________ cm
   BMI ___________

3. Have you consumed any medications in the past week (or any prescribed medications since completing the screening questionnaire)?
   If yes, please detail:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of occasions</th>
<th>Time since last used</th>
<th>Estimated dose</th>
</tr>
</thead>
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</table>

3. How many cups of coffee (or any other caffeinated drinks/products) have you consumed today? _____
   If > 0. How many hours since your last caffeinated drink _____ hours

4. Have you had any tobacco or nicotine products today? Yes / No
   If yes, how many cigarettes (or nicotine products) have you had today? _____
   If yes, How many hours since your last cigarette (nicotine product) _____ hours

5. What have you had to eat today? How long since you last ate something? ________ mins

6. Approximately how many hours sleep did you have last night? _____
1. What grade of school did you complete (up to year 12/secondary school)?
   Year _______

2. Have you completed any courses after school?
   No…………………………………0
   Yes, trade/technical……..1
   Yes, university……………….2
   Specify qualifications___________________________

3. Are you currently studying?
   No…………………………………0
   Yes, trade/technical………..1
   Yes, university……………….2
   Specify ___________________________

4. How are you currently employed? Mark ONE response
   Not employed ......................1
   Full time .............................2
   Part time/casual ....................3
   Full time student ....................4
   Home duties ........................5
   Work and study .................... 6
   Part-time student ..................8
   Other ...............................9
   Specify___________________________
Appendix D

Side Effect Checklist

During this experimental session have you experienced any of the following symptoms?

Yes      No
☐ ☐  headache
☐ ☐  nausea
☐ ☐  dry mouth
☐ ☐  runny nose
☐ ☐  sore throat
☐ ☐  nervous feeling
☐ ☐  dizziness

Are you currently experiencing any other adverse symptoms? Please specify.

_________________________________________
Appendix E

Visual Analogue Scales of Subjective Performance

Participant number:
Test point:

Please mark on each line at the point which most accurately reflects your level of agreement AT THE MOMENT with the below statement:

1. I feel alert

<table>
<thead>
<tr>
<th>STRONGLY AGREE</th>
<th>STRONGLY DISAGREE</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

2. I feel that I will be able to perform the attention tasks to the best of my ability

<table>
<thead>
<tr>
<th>STRONGLY AGREE</th>
<th>STRONGLY DISAGREE</th>
</tr>
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3. I do not feel that my driving would be impaired right now

<table>
<thead>
<tr>
<th>STRONGLY AGREE</th>
<th>STRONGLY DISAGREE</th>
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4. I feel capable of driving safely right now

<table>
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<tr>
<th>STRONGLY AGREE</th>
<th>STRONGLY DISAGREE</th>
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</table>
Visual Analogue Scales of Subjective Drug Effects

Participant number:  
Test point:  

Please mark on each line at the point which most accurately reflects your level of agreement AT THE MOMENT with the below statement:

1. Strength of drug effect

NO EFFECT  

Very Strong Effect

2. Liking of the drug effect

Dislike Very Much

Like Very Much

3. Alert level

Not Alert

Very Alert

4. Intoxication

Not Intoxicated

Very Intoxicated