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The Acute Effects of Nicotine and Exercise on Working Memory

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Abstract

Nicotine, an alkaloid found in tobacco leaves, has been used by humans for its psychoactive properties for centuries. Specifically, nicotine has been consistently shown to improve cognitive performance (Heishman, Kleykamp, & Singleton, 2010). Similar effects also have been shown with exercise (Chang, Labban, Gapin, & Etnier, 2012). The purpose of the present study was to examine whether a 20 min bout of moderate-intensity exercise enhances cognitive performance (working memory) as effectively as 4 mg of NICORETTE® gum in a non-smoker population. Twenty-three non-smokers (M age = 25.87; 13 female) underwent a three-week randomized counterbalanced procedure. The N-Back Task was used to measure working memory after administration of nicotine or exercise. Findings showed significant improvements in reaction time after both treatments. However, accuracy significantly improved only for exercise. The author recommends exercise over nicotine as a safe and effective strategy for non-smokers to enhance cognitive performance. Implications for future studies are discussed.

Keywords

Nicotine, Moderate-Intensity Exercise, Cognition, Working Memory, N-back
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Chapter One: Literature Review

1 Introduction

In the past couple years, Canadians have seen the amount of smokers aged 12 and older drop from 19.3% to 18.1% (Statistics Canada, 2014). This decline represented the lowest smoking rate reported since 2001. Smoking, however, remains a problem for 5.4 million Canadians and is the leading cause of preventable death (Why tobacco control is important, 2016). Furthermore, smoking is a risk factor for many diseases including lung cancer, heart disease, strokes and respiratory diseases (Surgeon General, 2014). Fortunately, smoking cessation can reduce the risk of these diseases and quitting has immediate and long-term health benefits. Within 12 hours of quitting one experiences improved lung function, blood circulation, and removal of carbon monoxide from the blood (Health Canada, 2012). Those who remain smoke-free for 15 years reduce their risk of coronary heart disease, and strokes to that of a non-smoker and reduce the risk of dying in half compared to those continuing to smoke. The problem does not lie in smokers’ desire to quit as 75% said they would quit when asked ‘If you could quit painlessly would you quit smoking or would you continue to smoke?’ (Mullins & Borland, 1996). Despite this, most quitters end up relapsing in the first eight days (Hughes, Keely, & Naud, 2004), while only 3-5% of unassisted quitters reach the one-year mark (CDCP, 2011). Disturbingly, almost half of lung cancer patients continue to smoke post surgery (Davison & Duffy, 1982; Walker et al., 2006), forty percent continue after undergoing laryngectomy (Himbury & West, 1985), and amongst those suffering a heart attack, forty percent relapse before leaving the hospital (Bigelow, Rand, Gross, Burling, & Gottlieb, 1986). These numbers indicate how challenging quitting is. This difficulty is not surprising as smoking has been known for its highly addictive nature since its introduction to the western world (Ferrence, Slade, Room, & Pope, 2000). Nicotine is one of the main culprits making smoking so addictive.
1.1 Nicotine Dependence

Nicotine acts as the principal psychoactive component in tobacco (Karan, Dani, & Benowitz, 2003). Cigarettes transport nicotine to the brain more efficiently than any other tobacco product as it delivers it to the brain within seven seconds of inhalation (Maisto, Galizio, & Connors, 2004). The average dose of nicotine each cigarette delivers is 1 to 2 mg of nicotine (Karan et al., 2003). Each smoker takes around 11 puffs per cigarette (USDHHS, 1988) and the average Canadian smoker smokes 13.9 cigarettes per day (Tobacco Use in Canada: Patterns and Trends, 2015) as the body metabolizes nicotine fairly quickly. Nicotine blood concentration levels can drop to half within two to three hours after smoking (Lynch & Bonnie, 1994).

Upon quitting, smokers experience a barrage of unpleasant signs and symptoms (Stolerman & Jarvis, 1995). Just after 12 hours of abstaining, smokers report cravings for tobacco, being irritable, cognitive impairments, restless, anxious, depressed mood, difficulty concentrating and increased hunger (Carruthers & Feyerabend, 1984; Bell, Taylor, Singleton, Henningfield, & Heishman, 1999; Gross, Javik & Rosenblatt, 1993; Hughes 1992; Hughes & Hatsukami 1986; Hughes, Hatsukami, Pickens, Krahn, Malin, & Luknic, 1984; Lyvers, Maltzman, & Miyata, 1994; West, Jarvis, Russell). These withdrawal effects manifest even after abstaining from nicotine chewing gum (West & Russell 1985; Hughes et al., 1986) further incriminating nicotine. Although it does not carry the same stigma, nicotine is as addictive as other drugs such as cocaine and heroin (USDHHS, 1988; SCOTH 1998; RCP 2000). Furthermore, nicotine meets the criteria for dependence (WHO, 1992) as it leads to tolerance, withdrawal, impaired control, neglect of activities, time spent in substance-related activity, continued use despite problems, and compulsion. The neurological effect of nicotine serves as a powerful driving force of this disorder; however, behavioural, genetic, and cognitive performance factors contribute as well. These are discussed in detail below.

1.2 Neurological factors

Nicotine’s substantial impact is partially due to its ability to imitate the role of the natural neurotransmitter acetylcholine and bind to the presynaptic nicotinic acetylcholine
receptors (nAChRs) in the brain (Di Matteo, Pierucci, Di Giovanni, Benigno, & Esposito, 2007). Upon binding, it releases many neurotransmitters including: glutamate (learning and memory enhancement), norepinephrine (arousal and appetite suppression) dopamine (reward-motivated behaviour), serotonin (mood and appetite modulation), and GABA (reduction in anxiety and tension Benowitz, 2008). Similar to other drugs and naturally rewarding stimuli like food, nicotine increases dopamine release in the nucleus accumbens (Brazell Mitchell, Joseph, & Gray, 1990; Benwell & Balfour 1992; Imperato, Mulas, & Di Chiara 1986; Rose & Corrigall 1997; Rowell Carr, & Garner, 1987; Salgado & Kaplitt, 2015). There is a substantial body of evidence indicating dopamine in the accumbens plays a prominent role in our reward system as it elicits euphoric feelings and reinforces future smoking behaviour (Benowitz, 2010; Wonnacott, Sidhpura, & Balfour, 2005). Alternating this pathway leads to abuse and addiction by causing an increase in sensitivity of the drug and decreased interest in non-drug stimuli (Melis, Spiga, & Diana, 2005). Moreover, lesions of the mesolimbic dopamine system weaken self-administration of nicotine (Corrigall et al., 1992). The role of nicotine in the accumbens is just one reason smoking is addictive.

1.3 Behavioural factors

The perceived cognitive benefits attained from smoking helps maintain the habit in many (West, 1993). Therefore, smokers might partake during stressful situations or whenever undergoing a lull. The intensity of one’s cravings and withdrawal symptoms can predict their relapse rate (Swan, Ward, & Jack, 1996). These cravings and withdrawal symptoms act analogous to an electric shock one receives as a form of punishment upon quitting and negatively reinforces the act of quitting (Eissenberg, 2004). The best way to alleviate/prevent this electric shock-cravings and withdrawal symptoms is to relapse and smoke. As the smoker learns these consequences they become conditioned to smoke, this type of learning is similar to operant conditioning (Skinner, 1963). As nicotine deprivation can negatively reinforce the habit; nicotine administration can positively reinforce smoking (Glautier, 2004). Six different species (rats, rhesus monkeys, squirrel monkeys, baboons, dogs and humans), have demonstrated that pure nicotine can serve as a positive reinforcer (Henningfield & Goldberg 1984; Stolerman 1987; Swedberg,
Henningfield, & Goldberg, 1990). Upon administration in humans, smoking is the unconditioned stimulus and cigarette cravings/withdrawal symptoms act as the unconditioned response, while neutral stimulus becomes drug-related cues (conditioned stimuli) and is parried with the drug and the hedonic drug effects it delivers (Pavlov, 1927). These conditioned stimuli can be situational cues like smoking while drinking coffee, cigarette smell and sight, and ashtrays or lighters. They can trigger cravings and withdrawal post pairing (Bevins & Palmatier, 2004; Niaura, 2000). Smokers quickly associate the act of smoking with pleasure and are motivated to perform this act anytime they are stressed or exposed to drug-related cues (Benowitz 2008; Gilbert 1995; Kassel, Stroud & Paronis 2003).

1.4 Genetic factors

The Cytochrome P450 2A6 (CYP2A6) encodes for an enzyme involved in the metabolic inactivation from nicotine to cotinine (Nakajima et al., 1996) and is a known candidate gene for smoking (Tobacco and Genetics Consortium, 2010). Different types of CYP2A6 metabolize nicotine at different speeds (Mwenifumbo & Tyndale, 2009). A slower metabolism is associated with lower prevalence of smoking and reduced cigarette use (Mwenifumbo & Tyndale, 2009; Ray, Tyndale, & Lerman, 2009). Smokers with the fast metabolism version of the gene smoke more and have their first cigarette earlier during the day. Furthermore, they report more intense withdrawal symptoms than those with slower nicotine metabolism (Kubota et al., 2006). Eight single nucleotide polymorphism around brain-derived neurotrophic factor (BDNF) are associated with smoking initiation (Tobacco and Genetics Consortium, 2010) and BDNF helps regulate synaptic plasticity and survival of cholinergic-dopaminergic neurons (Zhang, & Poo, 2001). Moreover, the prefrontal cortex and hippocampus have high levels of BDNF; these areas have implication in the cognitive enhancing effects of nicotine (Levin, McClernon, & Rezvani, 2006). Different genetic variations at BDNF might be altering the rewarding effects of nicotine by modifying the dopamine reward circuits and allowing the creation of drug-related memories that promote nicotine use after exposure. One single nucleotide polymorphism is associated with smoking cessations. Located 23 kb 5’ of DBH on chromosome 9 it accounts for 0.19% of the variance in smoking cessation (Tobacco and
Genetics Consortium, 2010). Three different loci have been associated with number of cigarettes per day; the SNP rs1051730 in CHRNA3 has the strongest association accounting for 0.5 of the variance. The SNP rs16969968 in CHRNA3, rs684513[G] in CHRNA5, and re9788682[G] and rs7163730[G] in LOC123688 also influence cigarettes per day independently.

1.5 Cognitive factors

Difficulty concentrating due to nicotine deprivation is a recognized symptom of nicotine withdrawal (Hughes, 2007) that leads to relapse and maintains smoking habits (American Psychiatric Association, 2000; Heishman, Taylor, & Henningfield, 1994). Furthermore, smoking eliminates these withdrawal-induced deficits (Heishman et al., 1994), and nicotine exposure increases alertness, vigor, and arousal (Gilbert, Dibb, Plath, & Hiyane, 2000; Perkins et al., 1994; Perkins, Grobe, Weiss, Fonte, & Caggiula, 1996). Abstaining from smoking negatively impacts working memory, sustained attention and response inhibition (Ashare, Falcone, & Lerman, 2014; Snyder & Henningfield, 1989), while cognitive impairs are detected just 4 hours of abstaining and could last more than nine days after the initial deprivation (Snyder & Henningfield, 1989). Hence, people that wish to quit face an uphill battle. Quitters deal with cravings, cognitive deficits, and withdrawal symptoms, which are all relapse factors, and the more intense, the faster the relapse (Swan et al., 1996). Expectedly, two-quarters of unaided quit attempts relapse within the first week (Hughes, 1992). Consequently, different smoking aids have been generated to aid quit attempts.

1.6 Quitting aids/treatments

Several quit-smoking aids are available for smokers to pick from (Lancaster, Stead, Silgay, & Swoden, 2000) such as: behavioural and psychological interventions (e.g. Cognitive-Behavioural Therapy, Exercise), Nicotine Replacement Therapy (NRT) (Lancaster et al., 2000), e-cigarettes (Brown, Beard, Kotz, Michie, & West, 2014) computer and other electronic aids (Chen et al., 2012), Exercise (Roberts et al., 2012) and pharmacological interventions (Antidepressants- nortriptyline, non-tricyclic antidepressant-Bupropion, nicotine receptor partial agonists-varenicline and cytosine).
The effectiveness of the different cessation strategies is shown in Table 1.

**Table 1: Percent Abstinent at Six Months for Smoking Cessation Strategies**

(USDHHS, 2008)

<table>
<thead>
<tr>
<th>Cessation strategies</th>
<th>% abstinent [95% CI]</th>
</tr>
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<tbody>
<tr>
<td>Physician advise to quit</td>
<td>10.2 [8.5, 12.0]</td>
</tr>
<tr>
<td><strong>Behavioural interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Proactive telephone counseling</td>
<td>13.1 [11.4, 14.8]</td>
</tr>
<tr>
<td>Group counseling</td>
<td>13.9 [11.6, 16.1]</td>
</tr>
<tr>
<td>Individual counseling</td>
<td>16.8 [14.7, 19.1]</td>
</tr>
<tr>
<td>Exercise-aided counseling</td>
<td>24.6 [15.78]</td>
</tr>
<tr>
<td><strong>Pharmacotherapy interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Nicotine patch (6 – 14 weeks)</td>
<td>23.4 (21.3, 25.8)</td>
</tr>
<tr>
<td>Nicotine gum (6 – 14 weeks)</td>
<td>19.0 (16.5, 21.9)</td>
</tr>
<tr>
<td>Nicotine lozenge (2 mg)</td>
<td>24.2(^a)</td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>24.8 [19.1, 31.6]</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>24.2 [22.2, 26.4]</td>
</tr>
<tr>
<td>Varenicline (2 mg/day)</td>
<td>33.2 [28.9, 37.8]</td>
</tr>
<tr>
<td>Vaccine</td>
<td>15.0 [20, 67](^{**})</td>
</tr>
<tr>
<td>Exercise aided nicotine</td>
<td>26.7(^{***a})</td>
</tr>
</tbody>
</table>

*Note. CI = Confidence Interval \(^a\)95% CI not reported. \(^b\)Three months for smoking cessation. * Marcus et al., 1999. ** Hartmann-Boyce, Cahill, Hatsukami, & Cornuz, 2012. *** Abrantes et al., 2014; Prapavessis, Cameron, Baldi, Robinson, Borrie, Harper, & Grove, 2007; Prapavessis, De Jesus, Fitzgeorge, Faulkner, Maddison, & Batten, 2016*

1.7 A closer examination of nicotine and cognition

A plethora of research has demonstrated nicotine’s ability to protect smokers from cognitive deficits during a quit attempt (Atzori Lemmonds, Kotler, Durcan, & Boyle 2008; Heishman, Kleykamp, & Singleton, 2010; Heishman, et al., 1994; Wesnes, Warburton, & Matz, 1983; West, 1993). This research, however, does not differentiate
whether nicotine only reverses cognitive deficits or improves cognitive performances (Heishman, Snyder, & Henningfield, 1993). Furthermore, smokers abstaining overnight might not be nicotine free as their plasma nicotine levels are as high as 5-10 ng/ml (Benowitz, Jacob, Jones, & Rosenberg 1982). This occurrence could explain why some studies failed to demonstrate nicotine’s benefits on cognitive performances (Grundey, Amu, Ambrus, Batsikadze, Paulus, & Nitsche, 2015; Kleykamp, Jennings, Blank, & Eissenberg, 2005; Myers, Taylor, Moolchan, & Heishman, 2008). There are three populations of interest worth examining to clarify this issue: not deprived smokers, minimally deprived smokers and non-smokers. In a 2010 meta-analysis conducted by Heishman and colleagues, the effects of nicotine on cognitive domains were assessed. The purpose of that study was to examine whether nicotine can improve cognitive performances and included studies with adult nonsmokers, smokers who were minimally deprived (less than 2 h), or smokers who were not deprived. The study included nine performance domains and out of those nine, six domains showed significant positive effects after administering nicotine: fine motor, alerting attention-accuracy and reaction time, orienting attention reaction time, short-term episodic memory-accuracy and working memory reaction time. These findings show that nicotine does not merely relieve cravings and related withdrawal symptoms in smokers; it also enhances cognitive performance in nonsmokers and not deprived smokers. These findings have been replicated in patients with schizophrenia, Alzheimer’s, ADHD, Parkinson’s diseases and other age-related cognitive declines (Evans & Drobes 2009; Levin et al., 2006; Newhouse, Potter, & Singh, 2004).

Nicotine may improve cognition via its ability to interact with the presynaptic nAChR receptors in the brain and aid the release of ACh, dopamine, serotonin, glutamate, and γ-aminobutyric acid (Heishman et al., 2010; Samuels & Davis 1998; Wonnacott 1997). These neurotransmitters are associated with learning and memory (Martin & Aceto, 1981). Specifically, the α7 and α4β2 nicotinic receptors found in the hippocampus of rats play a fundamental role in nicotine’s effect on cognitive functioning (Rezvani & Levin, 2001) and these receptors in the hippocampus and basolateral amygdala mediate nicotine’s role in memory (Levin et al., 2006; Mansvelder et al., 2006). Nicotine also increases hippocampal long-term potentiation (Hamid, Dawe, Gray, & Stephenson, 1997).
and facilitates hippocampal synaptic activity (Gray, Rajan, Radcliffe, Yakehiro, & Dani, 1996) causing the hippocampus to play an important role in nicotine’s effects on memory.

Nicotine activates several other brain regions involved in attention and memory including: the prefrontal cortex, parietal cortex, and thalamus (Azizian, Monterosso, O’Neill, & London, 2009; Brody 2006; Levin et al., 2006). Like the hippocampus, these areas are known to contain high densities of nAChRs. Levels of ACh increases in rats prefrontal cortex (PFC) in tasks that require attention (Himmelheber, Sarter, & Bruno, 2000; Passetti, Dalley, O'connell, Everitt, & Robbins, 2000). Nicotine administration activates the PFC in a similar manner as nAChr receptors are involved in PFC functions (Brody 2006; Levin et al., 2006; Azizian et al., 2009).

Nonsmokers receiving nicotine enjoy enhanced cortical facilitation as they experience cortical excitability (Grundey et al., 2015). Cortical excitability and plasticity are possible biomarkers for cognitive functioning (Miniussi & Ruzzoli 2013). Nicotine also alters norepinephrine and neural activity in the locus coeruleus, which is known to be part of the alerting/arousal network (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Posner & Rothbart 2007). Improvement in working memory performance in non-smokers is due to the enhancement of cortical excitability they enjoy post nicotine (Grundey, Freznosa, Klinker, Lang, Paulus, & Nitsche, 2013). Chronic nicotine administration leads to withdrawal upon cessation, which in turn leads to a down-regulation of the glutamate receptor function (Li, Semenova, D'Souza, Stoker, & Markou, 2014). The glutamate system is critically involved in working memory performances. Consequently, any down-regulation leads to performance deterioration in nicotine-deprived smokers (Driesen et al., 2013). Lastly, the glutamatergic system controls intracortical facilitation. Upon quitting, deprived smokers experience decreased intracortical facilitation (Grundey et al., 2013; Lang et al., 2008). Nicotine administration, however, restores compromised cortical facilitation returning it to baseline levels.

1.8 Exercise and cognition

Similar to nicotine, exercise enhances cognitive performances (Chang et al., 2012; Lambourne & Tomporowski, 2010; McMorris & Hale, 2012). Duration and intensity of
exercise play a role in determining the effects exercise will have on cognitive performances (Chang et al., 2012). Short exercise sessions (< 10 min) show a negligible effect while exercise bouts over 11 min show significant effects on cognitive performances. In general, it seems that 20 min of exercise is necessary to see enhancement. If the test is performed immediately after exercise, lighter intensity exercise will show these positive effects, however, if the delay is greater than 1 min between exercising and testing, very light exercise no longer shows any improvement while harder intensities (moderate or vigorous) show the most improvement. While the best cognitive improvements occur with moderate intensity (Kamijo, Nishihira, Higashiura, & Kuroiwa, 2007), the effects of exercise on cognitive performances might be an inverted-U as exercising until exhaustion leads to impairment on cognitive performance (Brown & Bray, 2014; Chang et al., 2012; Lambourne & Tomporowski, 2010; McMorris & Hale, 2012). Moderate-intensity exercise is known to show the best cognitive improvements (Kamijo et al., 2007; Gondola, 1987; Heckler & Croce, 1992; Sibley, Etnier, & Le Masurier, 2006; Tomporowski, 2003) and is easy enough to be done by untrained individuals.

Despite plenty of research being conducted on exercises and its effects on cognitive performances, studies examining its effects on smokers undergoing a quit attempt is limited. Self-reported evidence suggests poor concentration is reduced after engaging in 5 min (Daniel, Cropley, Ussher, & West, 2004) and 10 min (Ussher, Nunziata, Cropley, & West, 2001) of cycling or a 15 min brisk walk (Taylor & Katomeri, 2007). Only one study, however, has used objective measures in this population examining exercises effects on cognitive performance (Van Rensburg & Taylor, 2008). Van Rensburg & Taylor tested the effect of a 15 min self-paced walk on an attention task (Stroop colour-word interference task). Although participants in the exercise condition showed a reduction in desire to smoke, they did not see any improvement in cognitive functioning relative to passive controls. As no baseline measure of cognitive performance was taken while participants were still smoking, it cannot be deduced whether smokers performance declined as a function of abstinence and returned to baseline levels after exercise. Furthermore, participants were instructed to go on a brisk walk but were allowed to set the paced themselves. The lack of results could be due to the exercise intensity
participants chose to walk at. This pace could be insufficiently intense to impact cognitive functioning.

Increase in catecholamines (norepinephrine and dopamine) concentration due to exercise has been proposed to lead to faster processing (McMorris, Sproule, Turner, & Hale, 2011). Catecholamines activate the reticular formation and increase arousal. More specifically, P3 latency which measures the speed of stimulus classification and stimulus evaluation time (Kamijo et al., 2007), shows a decreased latency post exercise (Gerin & Privat, 1998; Travlos & Marisi, 1995). Decreased P3 latency plays a role in working memory RT partly explaining how exercise improves it.

Moderate-intensity exercise improves blood flow and oxygen to the brain (Ide & Secher, 2000) causing improvements in various cognitive tasks (Meeusen & De Meirleir, 1995; Polich & Kok, 1995). Exercise also improves cortical activation, which as aforementioned, is an important part of cognitive functioning. Exercise activates key brain areas associated with attention and memory performances. It was revealed that exercise activates dorsolateral prefrontal cortices in both hemispheres and the left dorsolateral prefrontal cortex during Stroop Test performances (Yanagisawa, Dan, Tsuzuki, Kato, Okamoto, Kyutoku & Soya, 2010). This activity correlated with improved performances on the test indicating exercises effect on cognition is partly mediated via enhanced prefrontal cortex activation. A study looking at brain activity during the N-back task post exercise showed increased brain activation in several brain regions (Li, Men, Chang, Fan, Ji, & Wei, 2014). Functional MRI showed increased activation in the right middle prefrontal gyrus, the right lingual gyrus, and the left fusiform gyrus and decreased activation in the anterior cingulate cortices, the left inferior frontal gyrus, and the right paracentral lobule during the harder task (2-back). Although there was a difference in brain firing post exercise, n-back scores were not significantly different. This could be attributed the study having a small sample size (n = 15). Furthermore, this study might have experienced a ceiling effect, as the 2-back task might not be hard enough. Lastly, there was greater activation in the brain during the 2-back condition compared to the 0-back condition. These brain regions are thought to be responsible for solving complex tasks.
Brain-derived neurotrophic factor (BDNF) plays an important role in neural development, functioning, neurogenesis and affects learning and memory performances (Szuhany, Bugatti, & Otto, 2015). This protein is found in high concentration throughout the central nervous system, including brain regions such as the hippocampus, cerebral cortex, hypothalamus and cerebellum (Murer Yan, & Raisman-Vozari, 2001). BDNF activity has been suggested to mediate the effects of exercise on cognition as it increases post exercise (Zoladz, Pilc, Majerczak, Grandys, Zapart-Bukowska, & Duda, 2008). Higher levels of BDNF have also been associated with improved cognitive task performances (Szuhany et al., 2015) while lower levels in older adults may contribute to memory impairments. Exercise-induced BDNF also reduces the threshold for encoding and memory (Intlekofer et al., 2013) putting the brain in a state of readiness for plasticity (Cotman, Berchtold, & Christie, 2007).

1.9 Working Memory

Working memory is an aspect of cognition worth focusing on as it plays a key role in goal-oriented behaviour and complex decision making (Baddeley, 1998; Bryan & Luszcz, 2001; Park, Smith, Lautenschlager, Earles, Frieske, Zwahr, & Gaines 1996). By interacting with the central executive mechanism, the phonological loop, and the visuospatial sketchpad (Baddeley, 1998), working memory provides temporary memorial representations. The phonological loop encodes verbal and acoustic info while the visuospatial sketchpad encodes visual and visuospatial information. The central executive is responsible for overseeing the whole process and ensuring information held in the short-term memory, and long-term memory is integrated. This study focuses on working memory as it plays a prominent role in everyday functioning (Heaton et al., 2004). For instance, working memory is needed for military, sport, and academic performance (Alloway, & Alloway, 2010; McMorris et al., 2011) and training working memory can improve fluid intelligence (Jaeggi, Studer-Luethi, Buschkuehl, Su, Jonides, & Perrig, 2010). Furthermore, exercise and nicotine are more likely to affect performances on working memory tasks than other simple cognitive tasks.
Several brain regions are consistently activated during n-back tasks including: the lateral premotor cortex, dorsal cingulate and medial premotor cortex, dorsolateral and ventrolateral prefrontal cortex, frontal pole and bilateral and medial posterior parietal cortex (Owen, McMillan, Laird, & Bullmore, 2005). These regions in general, implicate executive processes and performance in working memory tasks. Furthermore, the prefrontal cortex seems to have the biggest impact on working memory as several regions within the prefrontal cortex plays a prominent role in working memory performances.

Working memory is impacted negatively during a quit attempt (Jacobsen et al., 2007; Ashare et al., 2014; Snyder & Henningfield 1989) and nicotine can reverse the harmful effects of nicotine deprivation (Atzori et al., 2008; Ashare & McKee 2012). Nicotine administration and working memory research has produced equivocal findings. Some studies have shown positive effects in smokers (Ernst, Heishman, Spurgeon, & London, 2001; Grundey et al., 2015; Grobe, Perkins, Goettler-Good, & Wilson, 1998; McClernon, Gilbert, & Radtke, 2003; Myers et al., 2008) and non-smokers (Heishman et al., 2010; Kumari et al., 2003; McClernon et al., 2003; Mumenthaler, Taylor, O’Hara, & Yesavage, 1998), while others have shown no effects (Ernst et al., 2001; Foulds, Stapleton, Swettenham, Bell, McSorley, & Russell, 1996; Heishman et al., 1993; Hindmarch, Kerr, Sherwood, 1990; Kleykamp et al., 2005), and few have shown negative effects (Foulds et al., 1996; Grundey et al., 2015). There are currently no (a) standard nicotine dosages or form of administration and (b) uniformly accepted ways to assess working memory, which likely contribute to these inconsistent findings (Ernst et al., 2001). With respect to exercise, many studies have shown the positive effects of a single bout of exercise on working memory tasks (Churchill et al., 2002; McMorris et al., 2011; Williams & Lord, 1997); however, there is also no standard exercise dose (intensity and duration).

1.10 Nicotine vs. Exercise on Cognitive Performance (Working Memory)

As discussed above, nicotine has been shown to have a positive effect on cognitive performance in both smoking and non-smoking models, whereas exercise has been shown to have the same positive effect in non-smoking models only. There is no evidence that nicotine is superior to exercise in enhancing cognitive performance (i.e.,
working memory) in either smoking or non-smoking model.

1.11 Purpose and Hypothesis

Purpose
The purpose of the present study was to examine whether a 20 min bout of moderate-intensity exercise enhances cognitive performance (working memory) as effectively as 4 mg of NICORETTE® gum in a non-smoker population.

Hypothesis 1
All participants will improve working memory performance after nicotine and exercise treatment.

Hypothesis 2
There will be no significant difference in working memory performance between nicotine and exercise treatments.

1.12 Implications of this study

Nicotine’s effect on humans is undeniable. Aside from being an addictive psychoactive drug, it can also improve cognition. This cognitive boost could play a role in introducing non-smokers to smoking and even maintain this habit down the road. The cognitive effects of nicotine also impact special populations. Nicotine has been used to aid unhealthy populations to attenuate attention and cognitive deficits found in schizophrenia, Alzheimer’s, ADHD, Parkinsons’s diseases and other age-related cognitive decline (Evans & Drobes 2009; Levin et al., 2006; Newhouse et al., 2004). If exercise improves cognitive performance similarly to nicotine, it will gain support and credibility as a possible treatment aid for special populations while providing healthy non-smokers with a safe alternative.
Chapter Two: The Current Study

Ethics Statement
The experimental procedure was approved by the Western University Health Science Research Ethics Board (HSREB) and met the standards of the Declaration of Helsinki. Each participant was informed of the discomfort associated with acute exercise and nicotine before providing written informed consent.

2.1 Methods

Participants
The sample group for this study consisted of healthy male and female non-smokers (N=36). Participants were students from Western University and were recruited through posters placed across campus. Demographic data can be found in Table 2. Upon completion, participants received a $10 gift card to a local store. Inclusion criteria required participants be: (a) non-smoker; (b) aged 18-45 years; (c) right-handed; (d) have no contraindications to physical activity; and (e) no contraindications to nicotine. Exclusion criteria included: (a) dealing with a mental illness; (b) females who were pregnant or breastfeeding; (c) currently or recently smoked cigarettes; and (d) having major health complication. The 18-45 age range ensured this sample included the group with highest potential tobacco use (20-34 years) (Statistics Canada, 2014). Participants were removed from the dataset due to: dropouts (n=9), uncomfortable with nicotine (n=2), outside age criteria (n=1), and dealing with mental illness (n=1). The final sample size included twenty-three participants (M_{age} = 25.87, SD = 8.058. 13 female). Five reported smoking a cigarette at one point in their life, and only one was a previous smoker.

Design
This study employed a randomized, within-subjects counterbalanced procedure trial design. The sample was stratified by gender and was randomly assigned to conditions using a random number generator (www.randomizer.org). A graphic illustration of the study design can be found in Figure 2.

2.2 Primary Outcome Measure
Cognitive performance.
Working memory was measured using the N-back task (Jonides, Schumacher, Smith, Lauber, Awh, Minoshima, & Koeppe, 1997). The N-back task is a measure of working memory as it requires the use of both the phonological loop and the visuospatial sketchpad (Jonides et al., 1997). The N-back was performed on a laptop in an isolated room using INQUISIT By Millisecond Software (version 4.0.8.0). There were four different cognitive loads 0, 1, 2, and 3-back each increasing in difficulty. These loads occur in a random order. Each trial takes approximately 5 min to complete and involves a letter stimulus that appears on a computer screen for an interval of 500 ms, followed by a 1000 ms blank screen interstimulus. Participants see a total of 200 letters in the 5 minute task (0-back = 48 letters, 1-back = 48 letters, 2-back = 50 letters, 3-back = 54 letters). Participants had to determine if the stimuli matched the stimuli that appeared “N” items back and were instructed to press the response key (‘A’ key) using their right hand as soon as a target appears while keeping in mind both the speed and accuracy components of the task. In the 1-back condition, the target is defined as the letter stimulus that is the same as the one preceding it. For example, “x, interstimulus, x” would be the target. In the 2-back condition, the target is defined as a letter appearing that is the same as what preceded it two letters before. For example, “a, interstimulus, b, interstimulus, a”, would be the target (see Figure 1 for N-back illustration). The 3-back letter condition was treated as the primary outcome measure as it is most sensitive to behaviour and medication effects (Loughead et al., 2009). Performances on the N-back were assessed by recording the number of errors committed (Accuracy) and mean reaction time (RT) in milliseconds for each N-back condition. As previously mentioned, cognitive performance (working memory) was the focus of this study because it is affected by nicotine in both smokers and non-smokers (Kumari et al., 2003; Heishman et al., 2010) and exercise in non-smokers (McMorris et al., 2011). Furthermore, performances on the 3-back are influenced by acute exposure to nicotine (Heishman et al., 1994).
Figure 1. Diagram of the four N-back conditions (Braver, Cohen, Nystrom, Jonides, Smith, & Noll, 1997).

2.3 Other Measures

Vital signs
Heart rate and systolic/diastolic blood pressure were recorded to monitor the effect of nicotine gum and exercise. There were three measure points: before treatment, right after treatment, and after the N-back task. Heart rate was monitored using the Polar RS100 heart rate device and systolic/diastolic blood pressure was measured manually.

Sociodemographic Questionnaire
Information, including: age, gender, and contact information was collected.

Physical activity readiness questionnaire
The standard seven-item questionnaire was used to assess if participants required medical clearance to engage in physical activity (PAR-Q; Canadian Society for Exercise Physiology [CSEP], 2012). Participants were required to response yes or no to the questions; if they responded yes to any items they were ineligible to participate.

Smoking History & Current Practices
Participants past smoking history and habits were collected.
**Exercise Behaviour**

The Godin Leisure-Time Exercise Questionnaire was used to assess leisure-time physical activity (Godin, & Shephard, 1997). This brief four-item questionnaire breaks down the amount of mild, moderate and strenuous exercise participants engaged in during their free time and how often their heart beats rapidly.

**2.4 Intervention**

**Moderate-intensity exercise**

Moderate intensity was defined as 45 to 68% of heart rate. Moderate-intensity was calculated using the formula: \((220 – \text{age}) \times 60\text{–}70\% \) of heart rate, as this intensity improves multiple aspects of cognitive function (Chang, Tsai, Hung, So, Chen, Etnier, 2011; Hillman, Snook, & Jerome, 2003). Participants completed a 20 min bout of moderate-intensity exercise on a Woodway PPS treadmill (Woodway, Waukesha, WI). This bout entailed a 5 min warm up to start and 3 min cool-down to end. Participants’ heart rate was monitored closely using the Polar RS100 heart rate device. The researcher controlled the incline and speed corresponding to participants’ heart rate ensuring they were exercising at a moderate-intensity while allowing participants to decide whether they would rather have the speed or incline manipulated when needed. As previously mentioned this intensity of exercise has been shown to have the best results on cognitive performance including working memory (Kamijo et al., 2007 Gondola, 1987; Heckler & Croce, 1992; Sibley et al., 2006; Tomporowski, 2003). Moderate-intensity exercise is also easy enough to be done by untrained individuals.

**Nicotine gum**

Participants received two pieces of nicotine polacrilex (Nicorette®) gum. Each piece contained 2 mg of nicotine. Nicotine polacrilex was chosen due to ease of administration and controlled mean of delivery when administrated under the standardized chewing protocol (Henningfield, Radzius, Cooper, & Clayton, 1990). This protocol reduces individual response variability and plasma nicotine levels directly relate to the dose. Thus participants were instructed to chew once every 3 seconds for 20 min as almost 50% of the nicotine remains in the gum if not chewed properly (Benowitz, Jacob, & Savanapridi,
Lastly, nicotine gum was picked as it has low dependence potential and toxicity (USDHHS, 1988)

### 2.5 Procedure

Individuals who expressed interest and contacted investigators were screened for eligibility criteria by telephone or e-mail. Screening questions concerned smoking status, age, contraindications to nicotine or exercise, dominant hand, mental illness and for females current pregnancy or breastfeeding. If eligible, the researcher then scheduled the first lab visit. The study required participants to come to the Exercise and Health Psychology Laboratory (EHPL, www.ehpl.uwo.ca) at the University of Western (London, Ontario) for three sessions, baseline, first treatment, and second treatment.

Upon arriving at the lab, participants read the letter of information and offered signed consent followed by the sociodemographic questionnaire, PAR-Q, and Godin Leisure-Time Exercise Questionnaire. Participants were restricted to half a cup of coffee on each day of testing and instructed to abstain from alcohol and drugs for at least 24 hours before testing. Participants were then randomized into two equal treatment groups of either nicotine administration, or exercise participation, and then switch to counterbalance treatments. During baseline (Visit 1), participants were familiarized with the N-back task until they could consistently score 75% or higher in each N-back trial to eliminate any learning effect. Participants were instructed to perform the task as accurately as they can while keeping reaction time in mind. Once competency was established, a baseline cognitive measure was obtained from each participant utilizing the N-back test. Each visit was scheduled at seven days intervals, and participants were notified the night before testing as a reminder of instructions and protocol for the given task. Time of day that subjects participated in was kept constant. For the second visit, participants were randomized into one of two treatments (nicotine or exercise) and began the N-back immediately after treatment (within 2 min). Participants then returned for a third visit one week later and underwent the treatment condition (i.e. exercise or nicotine) they had not done yet. After completion of the third visit, participants were thanked and received their compensation (see Figure 2).
Figure 2. Flow diagram of participants moving through the study.

Recruited and initial screening

Baseline Visit:
Participants performed the n-back test

Visit 2:
Randomized into exercise treatment
Performed N-back post exercise

Visit 3:
Randomized into nicotine treatment
Performed N-back post nicotine

Visit 2:
Randomized into nicotine treatment
Performed N-back post exercise

Visit 3:
Randomized into exercise treatment
Performed N-back post nicotine
2.6 Statistical Analyses

**Manipulation check (treatment)**

Paired samples t-test was conducted to compare baseline heart rate and systolic/diastolic blood pressure to post-treatment heart rate and systolic/diastolic blood pressure.

**Primary outcome analyses**

Separate repeated measure MANOVAs (3 treatment conditions: baseline, nicotine, exercise) were conducted to examine the effects of treatment on N-back accuracy and RT. Significant main effects were followed by all possible pairways comparisons sample t-tests. MANOVA was chosen over ANOVA as the latter is susceptible to violations of sphericity (variances of the differences between all possible pairs of groups or conditions are equal) as indicated by Mauchly’s Test of Sphericity (Stevens, 1996).

The level of significance was accepted at $p < .05$ for all tests (Tabachnick & Fidell, 1996). Effect sizes ($\eta^2$) accompany all reported findings. In accordance with Cohen (1988), 0.02 is a small effect size, 0.13 is a moderate effect size, and 0.26 is a large effect size. Data was analyzed using IBM SPSS Statistics (Version 24).

<table>
<thead>
<tr>
<th>Variable</th>
<th>M</th>
<th>SD</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female)</td>
<td></td>
<td></td>
<td>56.52</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>25.87</td>
<td>8.06</td>
<td></td>
</tr>
<tr>
<td>Physical activity (Weekly frequencies)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strenuous</td>
<td>3.91</td>
<td>4.33</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3.43</td>
<td>2.63</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>2.09</td>
<td>2.04</td>
<td></td>
</tr>
<tr>
<td>Total weekly leisure activity (METs)</td>
<td>63.61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Bouts must be over 15 minutes*
2.7 Results

Manipulation Check

Exercise

Paired t-test showed that there was significant increase in heart rate \( t(22) = -13.855, p < .001, \eta^2=0.90 \) and systolic blood pressure \( t(21) = -6.074, p < .001, \eta^2=0.64 \) after engaging in moderate intensity from baseline to post-exercise. Diastolic blood pressure, however, was not significantly different \( t(21) = 1.125, p = .273, \eta^2=0.06 \).

Nicotine

Paired t-test showed that there was significant increase in heart rate \( t(20) = -5.545, p < .001, \eta^2=0.60 \) and diastolic blood pressure \( t(20) = -2.946, p = .008, \eta^2 = 0.30 \) after nicotine administration from baseline to post-exercise. Systolic blood pressure, however, was not significantly different \( t(20) = .169, p = .868, \eta^2 = 0.001 \).

Primary Outcome

3-Back Accuracy

Repeated measure MANOVA revealed a significant treatment effect on accuracy Wilks’ Lambda = .536, \( F(2, 21) = 9.104, p = .001 \), partial eta square \( \eta^2 = .464 \). These findings suggest that there was a change in accuracy across the 3 treatment conditions. Post-hoc comparison revealed a significant difference in the scores for baseline (\( M = 8.00, SD = 2.468 \)) and exercise (\( M = 5.52, SD = 3.043 \)) conditions—\( t(22) = 4.357, p < .001, \eta^2 = 0.46 \); no significant difference in the scores for baseline (\( M = 8.00, SD = 2.468 \)) and nicotine (\( M = 7.48, SD = 2.842 \)) conditions—\( t(22) = .866, p = .396, \eta^2 = 0.03 \) and; a significant difference in the scores for exercise (\( M = 5.52, SD = 3.043 \)) and nicotine (\( M = 7.48, SD = 2.842 \)) conditions—\( t(22) = 2.567, p = .012, \eta^2 = .25 \). (see Figure 3).

3-Back RT

Repeated measure MANOVA revealed a significant treatment effect on reaction time Wilks’ Lambda = .667, \( F(2, 21) = 5.232, p = .014 \), partial eta square \( \eta^2 = .333 \). These findings suggest that there was a change in RT across the 3 treatment conditions. Post-
hoc paired sample t-tests indicated that there was a significant difference in the scores for baseline (M=810.27, SD=209.801) and exercise (M = 710.64, SD = 181.948) conditions—\( t(22) = 3.204, p = .004, \eta^2=0.31; \) for baseline (M = 810.27, SD = 209.801) and nicotine (M = 708.99, SD = 187.469) conditions—\( t(22) = 3.099, p = .005, \eta^2=0.30; \) but not for exercise (M = 710.64, SD = 181.948) and nicotine (M = 810.27, SD = 209.801) conditions—\( t(22) = 0.087, p = .931, \eta^2= .00034. \) (see Figure 4).

Secondary Outcome

0-2 back

0-back accuracy. Repeated measures MANOVA revealed a non-significant treatment effect on reaction time Wilks’ Lambda = .937, \( F(2, 21) = .704, p = .506, \) partial eta square \( \eta^2 = .063. \)

1-back accuracy. Repeated measures MANOVA revealed a non-significant treatment effect on reaction time Wilks’ Lambda = .933, \( F(2, 21) = .755, p = .482, \) partial eta square \( \eta^2 = .067. \)

2-back accuracy. Repeated measures MANOVA revealed a non-significant treatment effect on reaction time Wilks’ Lambda = .785, \( F(2, 21) = 2.871, p = .079, \) partial eta square \( \eta^2 = .215. \)

0-back RT. Repeated measures MANOVA revealed a non-significant treatment effect on reaction time Wilks’ Lambda = .942, \( F(2, 21) = .647, p = .534, \) partial eta square \( \eta^2 = .058. \)

1-back RT. Repeated measures MANOVA revealed a non-significant treatment effect on reaction time Wilks’ Lambda = .800, \( F(2, 21) = 2.631, p = .096, \) partial eta square \( \eta^2 = .200. \)

2-back RT. Repeated measures MANOVA revealed a significant treatment effect on reaction time Wilks’ Lambda = .719, \( F(2, 21) = 4.105, p = .031, \) partial eta square \( \eta^2 = .281. \) These findings suggest that there was a change in RT across the 3 treatment conditions. Post-hoc paired sample t-tests indicated that there was a significant difference
in the scores for baseline (M=678.53, SD=204.390) and nicotine (M=618.56, SD=160.477) conditions—\(t(22)=2.932, p = .008, \eta^2=0.28\); but not for baseline (M = 678.53, SD = 204.390) and exercise (M = 638.30, SD = 233.344) conditions—\(t(22)=1.032, p = .313, \eta^2=0.046\); or for exercise (M = 638.30, SD = 233.344) and nicotine (M=618.56, SD = 160.477) conditions—\(t(22)=0.539, p = .596, \eta^2=.015\).

Table 3: Means, Standard Deviations, and 95% Confidence Intervals for 0-2 N-back

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean</th>
<th>SD</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-back RT</td>
<td>472.90</td>
<td>56.05</td>
<td>[448.66, 497.13]</td>
</tr>
<tr>
<td>1-back RT</td>
<td>551.76</td>
<td>127.56</td>
<td>[496.60, 606.92]</td>
</tr>
<tr>
<td>2-back RT</td>
<td>678.53</td>
<td>204.39</td>
<td>[590.145, 766.91]</td>
</tr>
<tr>
<td>0-back Accuracy</td>
<td>1.22</td>
<td>1.95</td>
<td>[.37, 2.06]</td>
</tr>
<tr>
<td>1-back Accuracy</td>
<td>.65</td>
<td>1.19</td>
<td>[.14, 1.17]</td>
</tr>
<tr>
<td>2-back Accuracy</td>
<td>2.87</td>
<td>2.44</td>
<td>[1.81, 3.92]</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-back RT</td>
<td>461.36</td>
<td>82.62</td>
<td>[425.63, 497.09]</td>
</tr>
<tr>
<td>1-back RT</td>
<td>536.53</td>
<td>160.91</td>
<td>[466.95, 606.12]</td>
</tr>
<tr>
<td>2-back RT</td>
<td>638.30</td>
<td>233.34</td>
<td>[537.39, 739.20]</td>
</tr>
<tr>
<td>0-back Accuracy</td>
<td>.78</td>
<td>1.62</td>
<td>[.08, 1.48]</td>
</tr>
<tr>
<td>1-back Accuracy</td>
<td>1.09</td>
<td>1.31</td>
<td>[.52, 1.65]</td>
</tr>
<tr>
<td>2-back Accuracy</td>
<td>1.87</td>
<td>2.75</td>
<td>[.68, 3.06]</td>
</tr>
<tr>
<td><strong>Nicotine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-back RT</td>
<td>469.15</td>
<td>118.42</td>
<td>[417.94, 520.35]</td>
</tr>
<tr>
<td>1-back RT</td>
<td>513.36</td>
<td>130.78</td>
<td>[456.81, 569.92]</td>
</tr>
<tr>
<td>2-back RT</td>
<td>618.56</td>
<td>160.48</td>
<td>[549.16, 687.96]</td>
</tr>
<tr>
<td>0-back Accuracy</td>
<td>1.57</td>
<td>2.98</td>
<td>[.27, 2.85]</td>
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<td>1-back Accuracy</td>
<td>1.00</td>
<td>1.28</td>
<td>[.45, 1.55]</td>
</tr>
<tr>
<td>2-back Accuracy</td>
<td>2.61</td>
<td>2.86</td>
<td>[1.37, 3.84]</td>
</tr>
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</table>
Figure 3. Mean accuracy scores at each time point. Error bars represent standard error. Each condition included 54 letter stimuli.
Figure 4. RT score at each time point. Error bars represent standard error.
Chapter Three: Discussion

To the author’s knowledge, this is the first study to investigate the effectiveness of an acute bout of moderate-intensity exercise versus 4 mg nicotine polacrilex gum on cognitive performance (i.e., working memory) in a non-smoking population. Participants underwent both treatments in a randomized counterbalanced fashion. Our main finding showed significant improvement in RT after both treatments. Accuracy significantly improved only for exercise. Beyond these general findings a number of specific issues warrant commentary.

Accuracy in the exercise condition improved by 31.25% but only 6.5% in the nicotine condition. This 26.4% net difference indicates that exercise was superior to nicotine in enhancing cognitive performance (i.e., working memory). Although previous literature supports exercise facilitating cognitive performance (Chang et al., 2012; Lambourne & Tomporowski, 2010; McMorris & Hale, 2012), the effects reported were smaller to the ones reported here. This raises the question why? One plausible reason is that the dose (i.e., duration = 20 minutes and intensity = 45-68% of heart rate) of exercise was optimal for enhancing cognitive performance in the present study. As previously mentioned, short exercise sessions (< 10 min) show negligible cognitive performance effects while exercise bouts over 11 min show significant effects (Chang et al., 2012). Superior cognitive improvements also have been shown with moderate intensity exercise (Kamijo et al., 2007). Fitness level seems to play a major role in exercises’ effect on cognitive performance (Chang et al., 2012) as highly fit participants appear to benefit the most while less-fit participants might suffer adverse effects. This is because unfit participants are more likely to reach exhaustion faster, which is associated with impaired cognitive performance (Brown & Bray, 2014). It is important to acknowledge that participants in this study were self-selected opening the possibility they exercise regularly or enjoy exercise. Finally, the N-back task that was selected to capture working memory accuracy may, in part, help explain these findings. Although past research has shown that the entire N-back protocol is sensitive to accuracy change by both acute exercise (Audiffren, 2009; Tomporowski, 2003) and nicotine (Heishman et al., 2010), the focus of the present study was on the 3-back (the most difficult and challenging task). It was suspected and
confirmed that 0-2 back conditions would be too easy for participants creating a ceiling effect, and thus negating treatment effects. The 3-back was also selected as it is sensitive to behavior and medication effects (Loughead et al., 2009). It should also be mentioned that the modest accuracy improvement found for nicotine is not consistent with effects reported for memory type tasks in the Heishman et al. (2010) meta-analysis.

RT improved by 12.34% in the exercise condition and 12.59% in the nicotine condition. This 0.25% net difference indicates that both treatments were equally effective in enhancing working memory RT. This finding is in line with previous literature. Past studies have typically reported large effect sizes for both exercise (Chang et al., 2012) and nicotine (Heishman et al., 2010). Furthermore, arousal has been shown to decrease RT (Eason, Harter, & White, 1969). Both treatments in this study are known to increase arousal (Fan et al., 2005; Gilbert et al., 2000; McMorris et al., 2011; Perkins et al., 1994; Perkins et al., 1996; Posner & Rothbart, 2007). Therefore, shorter RT is expected post-treatment.

Working memory tasks like the N-back provide accuracy and reaction time (RT) scores. Although there is a well-known speed-accuracy trade-off effect (performing a task faster jeopardizes its accuracy (Reed, 1973), this was not the case in either treatment as both showed decreased RT (12.34% for exercise and 12.59% for nicotine) while improving accuracy (31.25% for exercise and 6.5% for nicotine). The author argues accuracy data are more important in these types of tasks. Performing a cognitive task faster has little implication if accuracy is jeopardized. For example, it is more important to get the correct answer on an exam than to finish quickly.

Nicotine-induced enhancement might have been jeopardized as a consequence of dysphoria non-smokers experience (Heishman, et al., 1993; Hindmarch et al., 1990). Heishman and Henningfield (2000) sought to explore this idea by developing tolerance to the initial dysphoric effects of nicotine in non-smoker participants. Participants received ascending doses of nicotine (0, 2, 4, 8 mg) for eight consecutive days. At the end of the eight days, participants showed tolerance to the initial dysphoric effects of nicotine. Despite the tolerance manipulation, reaction time on working memory was the only
measure that improved while working memory accuracy, gross motor coordination, recognition, and visual scanning and attention were impaired. The findings from the present study suggests, any dysphoria non-smokers experience post nicotine is not adversely affecting cognitive task performances (i.e., accuracy). Furthermore, impairment seen in the Heishman and Henningfield study might have been due to the nicotine dose itself. Participants received 0, 2, 4, and 8 mg of nicotine gum causing plasma nicotine concentration levels to be as high as 6.9-11.5 ng/ml. Even after building tolerance, a 14 mg dose might be too high for non-smokers and could negatively impact cognitive performance.

3.1 Strengths and Limitations

There are several strengths that must be highlighted with the present study. First, a randomized counterbalanced trial design allowed every participant to undergo both treatments and serve as their own control. Using a randomized counterbalanced procedure guarded against practice or order of treatment effects. Furthermore, this design protected against any loss of motivation participants might experience causing them to try less in later visits. As this was a within-subject design, it had greater power and reduced error variance associated with individual difference (Pollatsek & Well, 1995). This in turn allowed the author to use a smaller number of participants to explore the effectiveness of the two treatments compared to a between subject design. Second, participants’ level of caffeine and alcohol consummation was controlled. Caffeine is known to increase feelings of concentration and alertness (Peeling & Dawson, 2007) and has been shown to enhance N-back performance depending on personality type-extraversion (Smillie & Gökçen, 2010). Alcohol is known to impair many types of cognitive function including working memory (Dry, Burns, Nettelbeck, Farquharson, & White, 2012). Additionally, coffee consumption can limit nicotine absorption (Henningfield et al., 1990). Ensuring these two were not consumed the day of testing (caffeine) and within 24 hours of testing (alcohol) played an instrumental role in assuring changes in performances were due to treatment rather than uncontrolled substance factors. Third, there was a manipulation check using HR and blood pressure data to ensure the two treatments were properly received. Past research shows nicotine significantly
increases diastolic blood pressure and heart rate (Ernst et al., 2001; Foulds et al., 1997; Hughes, Rose, & Callas, 2000; Ragueneau, Michaud, Démolis, Moryusef, Jaillon, & Funck-Brentano, 1999) while systolic blood pressure and heart rate increases due to exercise (Shahraki, Mirshekari, Shahraki, Shahraki, & Naroi, 2012). Lastly, the dose of 4 mg was picked, as 2 mg is not intense enough to produce all the physical symptoms of nicotine while stronger doses lead to higher reports of dysphoria (Kleykamp et al., 2005).

Despite the strengths highlighted, the present study is not without limitations. First, only one domain of cognitive performance (i.e., working memory) was examined. Thus it is unclear whether the effect is universal or only specific to working memory assessed through the N-back. Furthermore, although the N-back has strong face validity it has been shown to have weak convergent validity with other measures of working memory (Kirchner, 1958; Kane, Conway, Miura, & Colflesh, 2007). Second, with only twenty-three participants, these findings may not be generalizable to other non-smoking populations. Third, although participants were given specific chewing instructions, there is no way of knowing whether they followed instructions as they sat in a room alone for the 20 min. This is problematic as almost 50% of the nicotine remains in the gum with improper chewing (Benowitz, Jacob, & Savanapridi, 1987). However, although plasma nicotine levels were not recorded in this study, heart rate and diastolic blood pressure manipulation check indicate the nicotine treatment worked. N-back performances were enhanced post-nicotine further supporting this treatment. The question remains whether nicotine-induced improvements were maximized using the current procedure. If participants failed to follow the chewing procedure, they might have received enough nicotine to show a partial effect only. RT improved by 12.59% while accuracy only improved by 6.5%. These effects might underrepresent the effect of 4mg nicotine gum and further cognitive benefits could have resulted from the full dose. Fourth, neither the researcher nor the participant was blinded to the treatment. Fifth, this study did not measure the typical dysphoria or negative mood nicotine typically produces in non-smokers (Heishman et al., 1993). Sixth and finally, participants’ prior knowledge regarding treatment was also not measured. Hence, the author cannot rule out whether expectancy effects influenced the overall findings.
3.2 Future Directions

The results obtained in this study needs to be replicated with a larger non-smoking sample. An important future direction is conducting this study with a smoking population. Since abstinent smokers experience cognitive deficits, it would be interesting to see whether exercise-induced improvement is robust enough to reverse this impairment and show additional improvement.

As aforementioned, only one cognitive domain was examined. Future studies need to discover if exercise improves other domains more effectively than nicotine gum can. In the 2010 meta-analysis regarding nicotine’s effect on cognitive performances, thirteen domains were classified, and only six of those domains showed significant positive effects post administration (Heishman et al., 2010). Performances in all thirteen domains need to be examined post exercise. More importantly, the other five domains that improved post nicotine administration need to be tested post exercise to see which treatment is more effective on different types of cognition. Tasks like short-term episodic memory accuracy and alerting attention show the greatest improvement post nicotine administration making them potential candidates for future studies to examine.

Cognitive testing occurred immediately after treatment (approximately 2 min). This study did not examine whether treatment effects are present after a delay. Exercise has been shown to demonstrate its biggest effects on cognition 11-20 min after exercise, but these effects wane after delays longer than 20 min (Chang et al., 2012). Nicotine’s delayed enhancement effect has been observed in animal models and can last 24 h after administration (Buccafusco, & Jackson, 1991; Buccafusco, Jackson, Jonnala, & Terry, 1999). Nicotine’s delayed effect on human cognition, however, has yet to be examined. Future work needs to evaluate the effect of these two treatments in delayed testing models.

Another worthwhile line of inquiry is to clarify whether acute exercise and nicotine gum function through distinct mechanistic pathways. Imaging (brain scans) procedures may prove useful in identifying how exercise and nicotine exert their effect on cognitive performance. As previously mentioned, research has implicated overall cortical activity
in both treatments as one possible mechanism behind this effect (Grundey et al., 2013; Li et al., 2014; Yanagisawa et al., 2010). Correspondingly, enhanced intracortical facilitation in the prefrontal cortex is associated with improved working memory performance (Brunoni & Vanderhasselt, 2014), and there is a substantial amount of nicotinic receptors in the prefrontal functions. (Poorthuis & Mansvelder 2013). An advantage exercise has over nicotine is the ability to provide the brain with BDNF proteins which plays an essential role in learning and memory performances (Szuhany et al., 2015). This protein is released after exercise bouts and helps improve cognitive performances (Szuhany et al., 2015; Zoladz et al., 2008). There has been some evidence that nicotine administration leads to increases in BDNF mRMA expression in the dorsal hippocampus (Wei, Liu, Li, Zheng, Zhou, & Li, 2015). Evidence, however, remain minimal and more studies need to explore the role of nicotine and BDNF in human cognition.

Although the two treatments rely on the same brain region-prefrontal cortex-they could use different pathways allowing possible additive effect. With respect to additive effects, two studies have investigated the possibility of using acute exercise and NRT to alleviate cravings and withdrawal symptoms in a smoking model (Harper et al., 2012; Tritter, Fitzgeorge, & Prapavessis, 2015). Harper et al. found that combining acute exercise and the NRT patch led to extra cravings relief throughout the duration of the study (9 weeks post-quit). Withdrawal symptoms benefited from an additive effect up to the 7-week mark. This study, however, did not employ a control group leaving it open to criticism. The second study sought to validate this by adding a control group in an acute model. Smokers abstained for 15 h and were randomized into their conditions and receiving a 2 mg nicotine lozenge (Tritter et al., 2015). Those in the experimental condition partook in a 20 min moderate-intensity exercise bout while the control condition sat passively. The experimental group (which received both treatments) had lower craving scores at each time point. Withdrawal symptoms were reduced in both groups, but there was no evidence of any additive effect. This study did include a subjective assessment of concentration. Although this measure did improve, there was no visible additive effect of the two treatments. Future studies need to examine the possibility of any additive cognitive effects directly, as subjective reports are not always reliable. Furthermore,
concentration levels might experience a ceiling effect. Hence, a more sophisticated cognitive task is essential in exploring additive effects in future studies.

3.3 Implications

Nicotine has been suggested as medication in unhealthy populations dealing with cognitive deficits (Barr et al., 2008; White & Levin 1999; Wilson et al., 1995). This research indicates that exercise is a more effective and efficient treatment regarding cognitive functioning. Benefits of using a treatment like exercise include avoiding exposing these populations to an addictive drug like nicotine while exposing them to the countless health benefits exercise delivers (Clark & Uraina, 2011). Exercise enhances weight control, reduces the risk of cardiovascular disease, red type 2 diabetes, osteoporosis, as well as breast and colon cancers.

Young adult stress is associated with the decision to commence smoking (Byrne, Byrne, & Reinhart, 1995). This stress typically arises from school performance and future uncertainty, as academic success can determine future occupation. Consequently, adolescents turn towards smoking to help them cope. Alongside nicotine’s addictive effect, the cognitive boost it provides could reinforce this behaviour and help relief academic related stress if it translates to better grades. Moderate-intensity exercise can reduce stress (Hansmann, Hug, & Seeland, 2007; Jin, 1992) and has been shown to enhance cognitive performance (Chang et al., 2012). The findings from the present study can be used to convince the non-smoking population to look to healthy behaviours like exercise when facing stressful situations or cognitive lulls. Furthermore, smoking and exercising are incompatible behaviours as reported high leisure-time exercise levels are inversely related to smoking in self-reported surveys (Boutelle, Murray, Jeffery, Hennrikus & Lando, 2000). Therefore, exercising could further protect young adults from taking up smoking.

Eighty-five percent of Canadians do not meet the current Canadian Physical Activity Guidelines (Colley, Garriguet, Janssen, Craig, Clarke, & Tremblay, 2011) meaning most people are missing out on exercises-induced benefits in cognition and health in general. The results from this study might encourage people (students specifically) to begin
exercising to receive cognitive benefits. If regular exercise becomes habitual at a younger age, it could carry on into adulthood helping with the lack of exercise epidemic.

3.4 Conclusion

This is the first study directly examining the effectiveness of exercise and nicotine on cognitive performance (i.e., working memory) in non-smokers. Findings showed significant improvements in RT after both treatments. However, accuracy significantly improved only for exercise. The author recommends exercise over nicotine as a safe and effective strategy for non-smokers to enhance cognitive performance.
References


tobacco craving in drug abusers. *Nicotine & Tobacco Research, 1*(1), 45-52.


Canadian Society for Exercise Physiology. (2012). Physical activity readiness
questionnaire. Retrieved from
Center for Disease Control and Prevention (CDCP) (2011). Quitting smoking among
adults-- United States, 2001-2010. Morbidity and Mortality Weekly Report, 60,
1513-1519.
for smoking cessation: an overview and network meta-analysis. *The Cochrane
Library.*
Effects of acute exercise on executive function: a study with a Tower of London
Task. *Journal of Sport and Exercise Psychology, 33*(6), 847.
Churchill, J. D., Galvez, R., Colcombe, S., Swain, R. A., Kramer, A. F., & Greenough,
23(5), 941-955.
Colley, R. C., Garriguet, D., Janssen, I., Craig, C. L., Clarke, J., & Tremblay, M. S.
key roles of growth factor cascades and inflammation. *Trends in neurosciences,*
30(9), 464-472.
moderate versus light intensity exercise versus inactivity on tobacco withdrawal
Driesen, N. R., McCarthy, G., Bhagwagar, Z., Bloch, M. H., Calhoun, V. D., D'Souza, D.
C., ..., & Antićević, A. (2013). The impact of NMDA receptor blockade on human
working memory-related prefrontal function and connectivity. *Neuropsychopharmacology, 38*(13), 2613-2622.
visually evoked cortical potentials and reaction time in man. *Physiology &


Archives of general psychiatry, 43(3), 289-294.
Psychopharmacology, 83(1), 82-87.


Experimental Therapeutics, 270(2), 628-638.
psychiatry, 49(3), 258-267.


Taylor, A. H., Thompson, T. P., Greaves, C. J., Taylor, R. S., Green, C., Warren, F. C., ... & Campbell, J. (2014). A pilot randomised trial to assess the methods and
procedures for evaluating the clinical effectiveness and cost-effectiveness of Exercise Assisted Reduction then Stop (EARS) among disadvantaged smokers.


U.S.


Zoladz, J. A., Pile, A., Majerczak, J., Grandys, M., Zapart-Bukowska, J., & Duda, K.
Appendix A
Non-smoker volunteers needed for an exercise research study

We are examining the acute effect of exercise and nicotine on cognitive performance.
Participants must be:
Non-smokers between the age of 18 to 45
No mental illness or pregnancy
Able to perform moderate intensity aerobic exercise

Participants will receive a gift card as compensation for participating. Contact us if you would like to learn more about our study.

Exercise & Health Psychology Laboratory
Ethics Approval

Principal Investigator: Prof. Harry Praprotnik
Department & Institution: Health Sciences/Kinesiology, Western University

HSREB File Number: 106177
Study Title: The acute effects of nicotine and exercise on human cognition and working memory
Sponsor:

HSREB Initial Approval Date: April 20, 2015
HSREB Expiry Date: April 20, 2016

Documents Approved and/or Received for Information:

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The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00020490.

This is an official document. Please retain the original in your files.

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6G 1T9.  t. 519.661.3030  f. 519.660.2460  www.uwo.ca/research/ethics
Ethics Renewal

Western University Health Science Research Ethics Board
HSREB Annual Continuing Ethics Approval Notice

Date: March 18, 2016
Principal Investigator: Prof. Harry Papavasiliou
Department & Institution: Health Sciences/Kinesiology, Western University

Review Type: Full Board
HSREB File Number: 106177
Study Title: The acute effects of nicotine and exercise on human cognition and working memory

HSREB Renewal Due Date & HSREB Expiry Date:
Renewal Due - 2017/03/31
Expiry Date - 2017/04/20

The Western University Health Science Research Ethics Board (HSREB) has reviewed the Continuing Ethics Review (CER) Form and is re-issuing approval for the above noted study.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH E6 R1), the Ontario Freedom of Information and Protection of Privacy Act (FIPPA, 1990), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair
Ethics Officer to Contact for Further Information: Erika Bazile, Kathryn Hariri, Nicole Kamhi, Grace Kelly, Vikki Tran

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Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6G 1H9 t 519.661.3036 f 519.850.2466 www.uwo.ca/research/ethics
Letter of Information

Study Title: The Acute Effects of Nicotine and Exercise on Human Cognition and Working Memory

Principal Study Investigator:

Harry Prapavessis, Ph.D. (School of Kinesiology, The University of Western Ontario)

Co-Investigators:

Steven Guirguis, M.A. (School of Kinesiology, The University of Western Ontario)

Matthew Mancuso B.Sc. (School of Kinesiology, The University of Western Ontario)

Wuyou Sui, M.A. (School of Kinesiology, The University of Western Ontario)

You are being invited to participate in a research study looking at the effect of an acute bout of moderate intensity exercise and nicotine on cognitive performance. Cognitive performance describes people’s performance in tasks that require either memory or attention. This is a counterbalanced study (a type of research study in which each participant takes part in both groups and serves as their own control), which includes eligible volunteers who choose to take part. Please take your time to make a decision. The purpose of this letter is to provide you with the information you require to make an informed decision on participating in this research. This letter contains information to help you decide whether or not to participate in this research study. It is important for you to understand why the study is being conducted and what it will involve. Please take the time to read this carefully and feel free to ask questions if anything is unclear or there are words you do not understand. We are asking you to take part because you an adult between 18 and 65 years of age who does not smoke or have a history of smoking or mental illness. A total of 20 participants will be recruited for this study.

Invitation to Participate in Research and Eligibility Criteria

You are being invited to take part in this research study because you:

- are between the ages of 18 and 45
- Right-handed
- do not smoke or have a history of smoking
- do not have a mental illness
- are not pregnant
- do not have a medical condition that prevents you from exercising
- are able to read and write in English
- have a telephone or an email account that we can reach you
What is the purpose of this study?

It has been shown in past research that both exercising and nicotine can help improve cognitive function - intellectual processes by which one becomes aware of, perceives, or comprehends ideas.

In our study, we will be using an N-back computer task to measure working memory. The N-back task is a 5 minute task that displays a letter on a computer screen for an interval of 500ms, followed by a 1000ms blank screen interstimulus. You will have to click the left button of a computer mouse when a flashed letter on the screen is repeated with exactly one letter in between. For example, if the screen flashed X, then flashed another letter, then flashed X again, you would click the left mouse button (X here was the target letter).

The N-back has been used to measure aspects of cognitive functions. The main purpose of this study is to examine whether the improvements caused by acute aerobic exercise is comparable to those of nicotine.

WHAT ARE ASKED TO DO IN THIS STUDY?

If you choose to participate in this study, you will be asked to attend three laboratory sessions at the Exercise and Health Psychology Laboratory (EHPL) located at the Arthur & Sonia Labatt Health Sciences Building (HSB 408) in the University of Western Ontario. At the first meeting you will be asked to complete the Physical Activity Readiness Questionnaire (PAR-Q). Each laboratory meeting will take approximately 30 minutes and appointments will be arranged at your convenience and each appointment approximately a week apart. Following an outline for each laboratory session you will find detailed descriptions of each itemized task (1-4) that you will be asked to complete.

During your first session at the laboratory you will be asked to complete:

- Surveys (item – 1):
  - Demographic questionnaire (item – a)
  - Smoking history questionnaire (item – b)
  - Exercise behaviour in the last 7-days questionnaire (item – c)
- A cognitive computer task – N-back (item – 2)

During your second session at the laboratory you will be asked to complete:

- Surveys (item – 1)
- Pre-exercise or pre-nicotine (item – d)

- A treatment condition (item – 3), either:
  i) Moderate Intensity Aerobic Exercise or
  ii) Nicorette gum
During your third session at the laboratory you will be asked to complete:

- Surveys (item – 1):
  - Pre-exercise or pre-nicotine (item – d)

- A treatment condition (item – 3), either:
  i) Moderate Intensity Aerobic Exercise or ii) Nicorette gum

You are asked to abstain from alcohol for at least 18 hours prior to your laboratory meetings and restricted to 1/2 cup of coffee (item – 4).

The task descriptions are as follows:

1) Provide demographic and smoking and exercise information Time involvement = 20 minutes
The surveys will include:

   1. Demographic questionnaire (which asks you about information such as your age, education, marital status, income)
   2. Smoking history questionnaire (“What is the approximate date and time of the last cigarette you have smoked?”)
   3. Exercise behaviour in the last 7-days questionnaire (“In the last 7 days, how many times have you completed mild intensity exercise for 15 minutes or more?”)
   4. Pre-exercise/nicotine questionnaire will be filled out before completing either task

2) Participate in a cognitive computer task Time involvement = 15 minutes

3) Take part in treatment condition: i) Moderate Intensity Exercise or ii) Nicorette gum Time involvement = 20 minutes

i) Moderate Intensity Exercise (You will complete a single, 20-minute bout of moderate intensity exercise Exercise consisted of a 2-minute warm-up, followed by 15 min of walking at a rate, which will allow you to reach 2/3 of your max heart rate, and then a 3-minute cool down on a treadmill).

   a. Vital signs (heart rate and blood pressure) will be recorded just prior to, during, and immediately after exercise.

ii) Nicorette gum (will chew 2 pieces of polacrilex (Nicorette®) gum once every 3 seconds for 20 minutes)
   a. Vital signs (heart rate and blood pressure) will be recorded just prior to, and immediately after nicotine administration, and at the end of 20 minutes.
Note that you will perform both procedures (exercise, and Nicorette gum) by being randomized to one procedure first and then required to perform the other procedure 1-week later

4) Abstain from drinking alcohol/coffee for at least 18 hours

We ask that prior to your laboratory visit you abstain from drinking alcohol and restrict to 1/2 a cup of coffee for at least 18 hours.

What are the risks associated with my involvement in this study?

While in the study, you may experience side effects. Known side effects are listed below, but other effects, however unlikely, may occur that we cannot predict.

**Exercise:** There are some inherent risks of injury associated with exercise participation, particularly among people who are not used to exercising. You may, for example, feel mild muscle “tightness” or soreness that lasts for a couple of days. The possible benefits associated with exercise may outweigh the potential minor discomfort of beginning a supervised, laboratory-based exercise program. To minimize the physical risks of exercise, proper warm-up/cool-down and stretching protocols will be performed by a trained exercise counsellor. Additionally, the exercise program delivered will be tailored to your individual fitness level, and modified according to your comfort level. Furthermore, you will only be allowed to participate in this exercise program if you complete the PAR-Q (Physical Activity Readiness Questionnaire) forms to ensure that it is safe for you to begin an exercise program. The exercise facilitator will be both CPR and First Aid trained, and experienced in working with previously inactive populations. If any physical or mental risks arise during treatment The Student Emergency Response Team (SERT) will be available to provide immediate assistance. SERT will assist the exercise supervisor until the 911 emergency services arrive. Should you have a minor injury while exercising you will receive medical treatment onsite as necessary. A first aid kit and ice packs will be available for minor injuries.

**Nicorette® gum:** The primary side effects of lozenge use include: sore throat, heartburn, nausea/indigestion, and hiccups. People who experience any of the following symptoms should contact their doctor immediately: irregular heartbeat or heart palpitations, severe throat irritation, or mouth problems. Improper use of nicotine gum may put people in danger of developing a nicotine overdose. Overdose symptoms require immediate medical attention and include dizziness, weakness, diarrhoea, nausea, vomiting and a rapid heart rate. Prolonged use of nicotine gum may elevate a person’s risk of experiencing withdrawal symptoms upon ending treatment. Symptoms of withdrawal, such as nervousness, headache, irritability or tobacco cravings, can be uncomfortable. People should consult a physician to determine the best way to limit the risk or severity of withdrawal symptoms.

Do I have to take part?
Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care. If you decide to take part you will be given this Letter of Information to keep and be asked to sign the consent form. If you withdraw from the study, you maintain the right to request that any data collected from you not be used in the study. If you make such a request, all of the data collected from you will be destroyed. Please contact the study co-investigators, Steven Guirguis, Matthew Mancuso, or Wuyou Sui if you wish to withdraw from the study.

Participation in other studies

If you are participating in another study at this time, please inform the study researchers right away to determine if it is appropriate for you to participate in this study.

New findings

If, during the course of this study, new information becomes available that may relate to your willingness to continue to participate, this information will be provided to you by the investigator.

Are there any costs associated with participation?

You will receive a $10 gift card for participating in this study and will be provided with free parking for your visits to the laboratory if needed.

This study is covered by an insurance policy and if during the course of the study any injury should occur all medical expenses necessary to treat such injury will be paid provided: a) you comply at all times with the study researcher’s instructions b) you promptly report any such injury to the study researchers conducting the study, and c) the expenses are not otherwise covered by your provincial health care. Financial compensation for such things as lost wages, disability or discomfort due to this type of injury is not routinely available. You do not waive any legal rights by signing the consent form.

Will information obtained in the study be confidential?

All the information you provide to the researcher will be kept in the strictest confidence. You will be assigned an identification number and all data collected from you will be recorded and stored under this number only. Study researchers will not have any way of connecting your data to you. All data will be stored in coded form on computers accessible only to research staff in a secure office. You will not be identified in any documents relating to the research. No information obtained during the study will be discussed with anyone outside of the research team. If the results of the study are published, your name will not be used.
Representatives of the University of Western Ontario Health Sciences Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research. If we find information we are required by law to disclose, we cannot guarantee confidentiality. We will strive to ensure the confidentiality of your research-related records. Absolute confidentiality cannot be guaranteed, as we may have to disclose certain information under certain laws.

Questions?

If you have any questions about your rights as a research participant or the conduct of the study you may contact the Office of Research Ethics (Phone: 519-661-3036; Email: ethics@uwo.ca). If you have any questions about the study, please contact the study co-investigators, Steven Guirguis, Matthew Mancuso, or Wuyou Sui

This letter is for you to keep. You will be given a copy of this letter of information and consent form once it has been signed. If you have any concerns, please feel free to contact one of the researchers below. You may request the general findings of this research study from the researchers after the study is complete.

Dr. Harry Prapavessis Professor
School of Kinesiology, UWO

Wuyou Sui
M.A. Student
School of Kinesiology, UWO

Steven Guirguis
M.A. Student
School of Kinesiology, UWO

Matthew Mancuso
B.Sc. Student
School of Kinesiology, UWO

Informed Consent

Study Title: The Acute Effects of Nicotine and Exercise on Human Cognition and Working Memory

I have read the Letter of Information, had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction. I will be given a copy of the Letter of Information and consent form once it has been signed.

Consenting Signature:
Participant: ________________________________________________________
Please Print Name

Participant: ________________________________________________________
Please Sign Name

Date: ____________________

Please send me the overall conclusions from this trial: Yes □ No □

Researcher Signature:
Person obtaining informed consent:

Date: ____________________

_______________________________________
Please Print Name

_______________________________________
Please Sign Name
Appendix B
Sociodemographic Questionnaire

YOUR CONTACT INFORMATION:

First Name:_______________________  ...                 Last Name:___________________________ 

Home Phone: ________- _________-_________ 

Email Address: ____________________________________________@____________________ 

Date of Birth: __________/_________ 

MM           YYYY 

Study ID: ________________ 

EMERGENCY CONTACT INFORMATION:

First Name:_______________________  ...                 Last Name:___________________________ 

Day Phone: ________- _________-_________ 

ID:__________
Physical Activity Readiness Questionnaire (PARQ)

1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
   a. [ ] Yes
   b. [ ] No

2. Do you feel pain in your chest when you do physical activity?
   a. [ ] Yes
   b. [ ] No

3. In the past month, have you had chest pain when you were not doing physical activity?
   a. [ ] Yes
   b. [ ] No

4. Do you lose your balance because of dizziness or do you ever lose consciousness?
   a. [ ] Yes
   b. [ ] No

5. Do you have a bone or joint problem that could be made worse by a change in your physical activity?
   a. [ ] Yes
   b. [ ] No

6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart?
   a. [ ] Yes
   b. [ ] No

7. Do you know of any other reason why you should not do physical activity?
   a. [ ] Yes
   b. [ ] No
Section A – Smoking History & Current Practices

12. Have you ever smoked before? Yes/No

13. If yes, what is the approximate date and time of the last cigarette you have smoked?
   Date: ___________ Time: ___________

Section B – Exercise Behaviour: Godin Leisure-Time Exercise Questionnaire

1. During the last 7 days, how many times did you do the following kinds of exercise for more than 15 minutes during your free time (write on each line the appropriate number)?

   a) STRENUOUS EXERCISE (heart beats rapidly)
      (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling). ___________ times

   b) MODERATE EXERCISE (not exhausting)
      (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing). ___________ times

   c) MILD EXERCISE (minimal effort)
      (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking). ___________ times

2. During the last 7-Day period (week), in your leisure time, how often did you engage in any regular activity long enough that your heart would beat rapidly (work up a sweat)?

   1. Often _______  2. Sometimes _______  3. Rarely/Never _______
ID: __________

Nicotine

Date: __________

Have you abstained from alcohol in the past 24 hours? Yes No

Have you limited your consumption to 1/2 cup of caffeine today? Yes No N/A

Are you physically well today? Yes No

Initial HR __________

HR after gum __________

HR after N-back __________

Initial BP __________

BP after gum __________

BP after N-back __________
Exercise

Date:________________

Have you abstained from alcohol in the past 24 hours? Yes No

Have you limited your consumption to 1/2 cup of caffeine today? Yes No N/A

Are you physically well enough to be able to perform 20 minutes of moderate intensity exercise today? Yes No

Initial HR______________

HR at 10 minutes of exercise ________________

HR after exercise ________________

HR after N-back______________

Initial BP______________

BP at 10 minutes of exercise ________________

BP after N-back______________
Curriculum Vitae for Steven Guirguis

EDUCATION

- **Western University**
  - **London, ON**
  - **2014-Present**
    - Masters of Art (Thesis) in Kinesiology, Exercise and Health Psychology

- **McMaster University**
  - **Hamilton, ON**
  - **2010 – 2014**
    - Honors in Psychology, Neuroscience & Behaviour
      - Senior Honours Thesis: The effects of mental imagery training on self-control

TEACHING

**Teaching Assistant**

School of Kinesiology, University of Western Ontario

- **London, ON**
  - KIN 2250A - Social Foundations of Sport & Physical Activity 2014
  - KIN 2032B - Research Design in Human Movement Science 2015
  - KIN 1070A – Psychology of Human Movement Science 2015
  - KIN 2032B - Research Design in Human Movement Science 2016

CONFERENCES

**Poster Presentation**


**Oral Presentation**

- Guirguis, S., Sui, W., & Prapavessis, H. (2016). The Acute Effects of Nicotine and Exercise on Working Memory in Non-Smokers. Exercise is Medicine Ontario Student Research Conference [Accepted, will be published on Exercise is Medicine Canada].

RESEARCH EXPERIENCE

**The Smart Heart Trial**

- **London, ON**
- **September 2014 – Present**
  - Research Assistant
  - Collecting and entering data from bi-weekly fitness, body composition, and anthropometric testing in overweight children with operated heart defects.
  - Conducting stress tests, and DEXA scans.
  - Preparing and assessing physical activity.
NCIC Clinical Trials Group – Colon Health and Life-Long Exercise Change

**Physical Activity Consultant**

December 2014 – Present

- Conduct fitness testing, deliver physical activity intervention, monitor and track adherence, and provide behaviour support sessions with cancer survivors.

Be Healthy in Pregnancy (B-HIP)

**Research Assistant**

March 2015 – May 2016

- Conducting DEXA scans on 6-month-old infants and their mothers to examine how weight gain in mothers affects the infants.

The Child & Youth Network’s ACT-i-Pass Project

**Research Assistant**

March 2015 – May 2016

- Visiting local elementary school to conduct surveys with Grade 5 students.
- Developing focus groups meant to enhance the program for all involve (students, teachers, and parents).

Exercise and Health Psychology Lab

**Laboratory Manager**

May 2015 – Present

- In charge of all aspects of the lab, including contracts, equipment, supplies, software and documentation.

Exercise at Western

**Research Assistant**


- Supervising participants as they exercise in the EHPL.
- Conducting fitness assessments (stress tests, workout assessment, and DEXA scans) on participants at 6m, 9m, and 12m.

Ribcage Injuries in Olympic Women Rowers

**Lab Technician**

November 2015

- Conducting DEXA scans on the Canadian Olympic Women’s rowing team.

VOLUNTEER EXPERIENCE

**Special Olympics London**

Assistant Coach

December 2015 – Present

- October 2009 – May 2013
- October 2009 – April 2011
- September 2011 – May 2013

**STM – Basketball League**

Head Coach

League Commissioner

PROFESSIONAL AFFILIATION

- North American Society for the Psychology of Sport and Physical Activity (NASPSPA)
- Canadian Society for Psychomotor Learning and Sport Psychology (SCAPPS)

ADDITIONAL QUALIFICATIONS

- *Trained to operate a Metabolic Cart, Interpret data, and create exercise prescriptions. Able to conduct Spirometry and Peak VO2 assessments.*
- *Trained to operate Dual-Emission X-ray Absorptiometry and interpret accompanying data. Able to operate iDXA body composition scans.*
- *Standard First Aid CPR/AED Level C. Canadian Red Cross*