Dopamine receptor (DRD2) genotype-dependent effects of nicotine on event-related potential indices of attention during rapid visual information processing

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(Behavioural Neuroscience Specialization)

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ABSTRACT

The attention-augmenting effects of nicotine and dopaminergic involvement in these effects have been demonstrated in many studies. In an attempt to further characterize the mechanisms underlying dopaminergic function in response to nicotine, this study examined the role of the dopamine D2 receptor (DRD2) TaqIA polymorphism in nicotine's attentional effects as the presence of the A1 allele of this polymorphism has been associated with dependence and reduced attentional tone. More specifically, the P300, an event-related potential (ERP) index of attention was assessed in 24 healthy non-smokers performing a rapid visual information processing (RVIP) task following acute nicotine or placebo gum administration. Although nicotine increased subjective alertness and heart rate, it did not enhance RVIP performance and there were no differences between genotype groups. Although the results do not accord with previous research in smokers, it is not inconsistent with those studies involving non-smokers and suggest smoker-status dependent differential effects of genotype on nicotine responsivity.

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LIST OF ABBREVIATIONS

ANOVA	analysis of variance
ANCOVA	analysis of covariance
5-HT	5-hydroxy-tryptophan (serotonin)
5-HTT	serotonin transporter
BOLD	blood oxygen level dependent
CNS	central nervous system
COMT	catechol-O-methyltransferase
CPP	conditioned place preference
CPT	continuous processing task
DA	dopamine
DAT	dopamine transporter
DRD1	dopamine D1 receptor
DRD2	dopamine D2 receptor
DRD4	dopamine D4 receptor
EEG	electroencephalogram
EOG	electro-oculogram
EPQ	Eysenck personality questionnaire
ERP	event-related potential
fMRI	functional magnetic resonance imaging
GABA	gamma amino butyric acid
GVG	gamma vinyl GABA
MAO	monoamine oxidase

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MLA	methyllycaconitine
NAcc	nucleus accumbens
nAChR	nicotinic cholinergic receptor
NMDA	N-methyl-D-aspartate
PCR	polymerase chain reaction
PET	positron emission tomography
PFC	prefrontal cortex
RFLP	restriction fragment length polymorphism
RVIP	rapid visual information processing
SNP	single nucleotide polymorphism
SPECT	single photon emission computed tomography
SPET	single photon emission tomography
SSS-V	sensation seeking scale version V
UTR	untranslated region
VTA	ventral tegmental area

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1.0 Introduction

Although the incidence of smoking has declined in recent years, 20-25% of North Americans continuing to smoke on a regular daily basis (Center for Disease Control and Prevention, 1999; Health Canada, 1999). Smoking is associated with significant health risks, including heart disease, emphysema, and premature morbidity and is considered to be the most preventable cause of cancer, resulting in substantial societal, economic, and individual costs. Although the detrimental effects of smoking are well known, the neurobiological mechanisms underlying the addiction are not.

Nicotine is the principle psychoactive/addictive component in cigarettes as evidenced by the fact that animals will actively seek (Corrigall, 1999; Di Chiara, 2000) and self-administer (Corrigall, 1999; Rose & Corrigall, 1997) it. In rats, pronounced conditioned place preference (CPP) is also induced by nicotine, consistent with its putatively rewarding effects (Le Foll & Goldberg, 2005). Furthermore, smoking cessation is associated with symptoms of withdrawal which are extinguished with nicotine replacement (Stolerman & Jarvis, 1995). Nicotine is readily self-administered in humans (Pomerleau & Pomerleau, 1992) and many other mammalian species (Donny, Cagguila, Knopf, & Brown, 1995; Goldberg, Spealman, & Goldberg, 1981; Valentine, Hokanson, Matta, & Sharp, 1997). The quantity of cigarettes smoked tends be related to maintenance of constant nicotine levels in dependent smokers (Russell, et al., 1995). Despite the fact that a majority of smokers attempt to quit, only 3% succeed (Li, 2006), further supporting the addictive nature of nicotine.

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1.1 Neurobiology

1.1.1 Cholinergic System and Nicotine

Neurobiologically, nicotine is thought to exert its rewarding and aversive effects both directly and indirectly. It acts directly on nicotinic acetylcholinergic receptors (nAChR), the primary function of which in the central nervous system is to modulate neurotransmitter release (Wonnacott, 1997). Consistent with this, nicotine stimulates the release of most neurotransmitters in many areas throughout the brain (McGehee, Heath, Gelber, Devay, & Role, 1995; McGehee & Role, 1995; Gray, Rajan, Radcliffe, Yakehiro, & Dani, 1996; Role & Berg, 1996; Grady et al., 2001; Kenny, File, & Neal, 2000; Alkondon, Pereira, Barbosa, & Albuquerque, 1997; Wilkie, Hutson, Sullivan, & Wonnacott, 1996; Albuquerque, Pereira, Alkondon, Schrattenholz, & Maelicke, 1997), including dopamine, GABA, glutamate, serotonin and noradrenaline (Watkins, Koob, & Markou, 2000).

It is thought that nicotine, via nAChR stimulation, regulates the activities of the mesolimbic dopamine (DA) reward pathway as cholinergic stimulation of the ventral tegmental area (VTA) increases DA concentration in the nucleus accumbens (NAcc), while cholinergic antagonists reduce DA concentration (Blaha et al., 1996; Ernhardt, Schwieler, & Engberg, 2002), and nicotine-induced DA release in the rat NAcc appears to be regulated by nAChRs in the VTA (Nisell, Nomikos, & Svensson, 1994a). Nicotinic AChRs are pentameric ligand-gated cation channels, comprised of combinations of the twelve known subunit types, with the heteromeric $\alpha 4\beta 2$ and the homomeric $\alpha 7$ receptors being the most common (Hoyle, Genn, Fernandes, & Stolerman, 2006). The use of knockout mice (i.e., mice in which a gene of interest is made inoperable, thereby

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allowing greater understanding of the normal functioning of that gene) has enabled the identification of both the most commonly occurring subunits, α4, α7, and β2 (Flores, Rogers, Pabreza, Wolfe, & Kellar, 1992; Zoli, Picciotto, & Changeux, 1998) and the nAChR subtypes responsible for nicotine-induced increases in DA (Picciotto & Corrigall, 2002). The subunit composition of nAChRs has demonstrated relevance in the subsequent activation of downstream dompaminergic circuitry (Picciotto, Zoli & Changeux, 1999; Piccioto & Corrigall 2002), as the presence of the β2 subunit appears to be required to modulate the excitability of the DA neurons (Picciotto & Corrigall, 2002; Picciotto, Zoli & Changeux, 1999), and receptors containing the α4 and β2 subunits have been related to the stimulant-like and rewarding effects of nicotine (Grottick et al, 2000; Jones & Benowitz, 2002). Implicating the α7 AchRs nicotine-induced DA increases in the NAcc have been shown to be blocked by the α7 AChR antagonist methyllycaconitine (MLA) (Schilstrom et al., 2000). Furthermore, chronic cigarette smoke exposure in rats increased the number of nAChRs in the striatum, cortex and cerebellum with no change in the affinity of the receptors for nicotine (Yates, Bencherif, Fluhler, & Lippiello, 1995) and chronic infusion of both nicotine and mecamylamine (nAChR antagonist) increased the number of nicotine binding sites as evidenced by autoradiography in mice, suggesting the same receptor numbers are activated by either agonist or antagonist application (Pauly, Marks, Robinson, van de Kamp, & Collins, 1996). A seemingly contradictory result, the nicotine-induced nAChR upregulation may be explained by desensitization of nicotinic receptors following chronic nicotine exposure (Marks, Burch & Collins, 1983; Schwartz & Kellar, 1985) and this is supported by the finding that nAChRs are upregulated following chronic nicotine exposure in cultured rat cortical cells (Yates et al.,

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1995). It has been suggested that with chronic nicotine use, neuroadaptations of these various neurotransmitter systems contribute to dependence and withdrawal. (Kenny, & Markou, 2001; Watkins, Koob, & Markou, 2000).

Post-mortem analyses of smokers indicated an increased nAChR density relative to non-smokers, which may indicate either a pre-existing state or a neuroadaptation to smoking (Benwell, Balfour, & Anderson, 1988). This increase, however, does not appear to be the result of increased translation, as mRNA (coding for the α4 and β2 subunits) levels remained constant, implying that other mechanisms, possibly post-translational, may be involved (Pauly et al., 1996). Furthermore, postmortem studies have indicated increased nicotine binding, particularly in the hippocampus and thalamus in long term smokers (but not in ex-smokers) and this increase, thought to be due to increased nicotine receptor numbers, may be an antecedent condition or consequence of smoking and may play a role in nicotine tolerance and addiction (Breese et al., 1997). This contention is supported by rodent studies which found a genetic basis for number of nAChRs (Collins & Marks, 1991) and a significant strain-dependent response to acute nicotine (Marks, Stitzel, & Collins, 1989).

1.1.2. Dopaminergic System and Nicotine

The dopaminergic system has been repeatedly associated with the reinforcing properties of many drugs as well as mediating a number of functions including cognition, emotion, motor and endocrine control (Wickens, 1990). A number of drugs of abuse, including opiates, ethanol, amphetamine, and nicotine, have been found to increase extracellular DA concentration in the NAcc and dorsal caudate nucleus of rats, while drugs with aversive properties reduced DA concentration in these areas (Di Chiara, &

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Imperato, 1988). Consistent with this, DA turnover is greatest in the NAcc (relative to other brain regions) following acute nicotine administration (Lapin, Maker, Sershen, & Lajtha, 1989) and upon activation, midbrain cholinergic neurons, particularly those arising in the laterodorsal tegmental nucleus and the pedunculopontine tegmental nucleus (a major source of VTA innervation) trigger DA release in ascending mesolimbic and mesocortical dopaminergic pathways (Laviolette & van der Kooy, 2004). Lesioning or microinfusion of nAChR antagonists to the pedunculopontine tegmental nucleus has resulted in reduced nicotine self-administration in rats (Lanca, Adamson, Coen, Chow, & Corrigall, 2000), implicating its involvement in reward. The mesolimbic pathway involves DA release from midbrain neurons of the VTA, which project to the nucleus accumbens (NAcc) (Laviolette & van der Kooy, 2004). In the mesocortical path, dopaminergic neurons project to and trigger DA release in the prefrontal cortex (PFC) (Watkins, Koob, & Markou, 2000), a region known to be associated with attentional processing. Furthermore, DA release in this area is also induced in response to stress (Inglis, & Moghaddam, 1999; Deutch, & Roth, 1990).

The integral role played by the VTA and the NAcc in both the reinforcing and the aversive properties of many drugs (including nicotine) is apparent in that the direct application of many drugs to the VTA induced both reward and aversion (Laviolette, & van der kooy, 2003). In addition, VTA DA neurons displayed increased firing and burst activity with (i.v.) nicotine administration indicating increased activation of neurons associated with the reward pathway (Grenhoff, Aston-Jones, & Svensson, 1986; Mereu et al., 1987; Nisell, Nomikos, & Svensson 1995). Both acute and chronic nicotine administration increased extracellular DA in the NAcc (Dewey et al., 1999) and

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cholinergic stimulation of the VTA (Blaha et al., 1996; Damsma, Day, & Fibiger, 1989; DiChiara & Imperato, 1986; Nisell, Nomikos, & Svensson 1994a, 1995; Pontieri, Tanda, Orzi, & DiChiara, 1996) or nicotine application to the NAcc increased both extracellular DA and its metabolites in the NAcc and this state may persist for hours (Benwell & Balfour, 1992; Nisell et al., 1994a). This is also evidenced in vitro, as nicotine stimulates DA release in striatal and accumbal slices (Chesselet, 1984; Rowell, Carr, & Gardner, 1987) and electrically-induced DA release is maximal in the NAcc and lowest in the VTA (DiChiara, & Imperato, 1988; Pontieri, Tanda, Orzi, & Di Chiara, 1996; Sziraki et al., 2001). Further support for the role of midbrain dopaminergic and cholinergic neurons in the rewarding actions of nicotine is evident in diminished nicotine self-administration following: the application of a nAChR antagonist (mecamylamine) to the VTA in mice (David, Besson, Changeux, Granon & Cazala, 2006); the application of dihydro-β-erythrodine (an irreversible DA receptor antagonist) to the VTA (Corrigall, 1999; David et al., 2006; Di Chara, 2000), and lesions to the DA neurons of the VTA (Wise & Bozarth, 1987). In addition, these manipulations were found to reduce nicotine-induced increases in locomotor activity (Clarke, Fu, Jakubovic, & Fibiger, 1988). However, concomitant infusion of nicotine and mecamylamine to the VTA had no effect on DA levels in the NAcc (Nisell et al., 1994a; Corrigall, Coen & Adamson, 1994) nor did partial lesions of the pedunculopontine tegmental nucleus (Corrigall, Coen & Adamson, 1994). It has been suggested that together, these findings implicate neuronal sensitivity to nicotine and endogenous DA levels as being critical modulatory factors in nicotine dependence (Sziraki et al., 2001).

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With respect to dopamine receptors, smokers (relative to nonsmokers) display reduced dopamine D1 receptor (DRD1) binding in the ventral striatum, although whether this contributes to or results from smoking is unclear (Dagher et al., 2001). The specific involvement of both DRD1 and dopamine D2 receptors (DRD2) in the rewarding effects of nicotine is supported by the attenuation of nicotine self-administration following the application of DRD1 and DRD2 antagonists (Corrigall & Coen, 1991; Corrigall, Franklin, Coen, & Clarke, 1992) and by elimination of DA release in the NAcc following antagonism of DRD2 receptors (Sziraki, Sershen, Hashim, & Lajtha, 2002). In addition, chronic smoking has been shown to upregulate DRD1 and DRD2 mRNA expression in the ventral striatum (Bahk, Li, Park, & Kim, 2002), while acute nicotine or smoking has been shown to upregulate dopamine transporter (DAT) mRNA expression in the VTA and substantia nigra (Li et al., 2004), further suggesting DA receptor function involvement in smoking.

Neuroimaging studies also support dopaminergic involvement in smoking behaviour, as positron emission tomography (PET) studies have shown nicotine administration resulted in striatal DA release in non-human primates (Tsukada et al., 2002), stimulated regional glucose metabolism in rats and autoradiography evidenced increased DA neurotransmission in the NAcc (Pontieri et al., 1996). Furthermore, single photon emission computed tomography (SPECT) studies have revealed that smokers had significantly lower striatal DA transporter densities relative to nonsmokers (Krause et al., 2002) and, although strain dependent, nicotine decreased electrically-induced DA release in frontal cortical slices and increased DA release in ventral tegmental slices in rat microdialysis studies (Sziraki et al., 2001). In a review of neuroimaging studies, Brody

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(2006) concluded that there is support for enhanced activity of cortico-basal ganglia thalamic circuitry following acute nicotine or smoking. This review also supported DAergic involvement in nicotine's effects, as it suggested that the enhanced neurotransmission may be either a direct result of nAChR activity or an indirect result of increased DAergic function and that these alterations may be responsible for a number of nicotine's effects, including attentional augmentation and mood elevation.

1.1.3. Gamma Amino Butyrtic Acid (GABA) System and Nicotine

While there is a substantial support for the involvement of the midbrain cholinergic and DAergic systems in smoking, it is critical to note that they do not operate in isolation, as multiple neurotransmitter systems have been implicated in mediating the relationship between nicotine and it's rewarding effects. In addition to altering dopaminergic function, nicotine's actions on nAChRs also appear to have consequences in GABAergic neurotransmission, the primary inhibitory system in the central nervous system. VTA DA neurons receive inhibitory GABAergic input from local interneurons and projection fibres from the NAcc and ventral pallidum (Kalivas, Churchill, & Klitenick, 1993; Steffensen, Svingos, Pickel, & Henriksen, 1998). GABA neurons express excitatory nAChRs throughout the brains of rodents and humans (Alkondon, Pereira, Eisenberg, & Albuquerque, 2000; Fisher, Pidiplichko, & Dani, 1998; Jones & Yakel, 1997; Lena & Changeux, 1997; Lena, Changeux, & Mulle, 1993) and it is thought that the altered/increased VTA dopaminergic activity (and subsequent DA release in the NAcc) in response to nicotine is mediated in part by desensitization of inhibitory GABAergic circuitry (Ernhardt, Schweiler & Engberg, 2002) as administration of a $GABA_B$ receptor agonist attenuated or eliminated nicotine-induced accumbal DA

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increases (Fadda, Scherma, Fresu, Collu, & Fratta, 2003; Dewey et al., 1999) and $GABA_A$ antagonist application led to increased DA release and increased behavioural reinforcement (Mansvelder, Keath, & McGehee, 2002; Ikemoto, Kohl, & McBride, 1997). In smokers, a $GABA_B$ receptor agonist did not decrease the number of cigarettes smoked or reduce craving, but did increase subjective experience of nicotine's aversive properties (Cousins, Stamat, & de Wit, 2001) suggesting that GABAergic signaling mediates some, but not all of nicotine's effects. Gamma vinyl GABA (GVG), an inhibitor of GABA transaminase (an enzyme which prevents the metabolism of GABA), impaired both acute and chronic nicotine-induced increases in NAcc DA, which is consistent with the proposition that increased GABAergic function reduces DA in the NAcc (Dewey et al., 1999). Primate PET studies indicated that DA receptor availability is reduced following nicotine exposure and pretreatment with GVG attenuated this effect (Dewey et al., 1999). Behaviourally, this is evidenced by the abolishment of a nicotine-induced CPP response in rats following GVG administration, suggesting that GVG may block the reinforcing properties of nicotine (Dewey et al., 1999) which may be related to increased DA release in the NAcc. It is thought that nicotine transiently enhances and then, via nAChR desensitization, subsequently reduces GABAergic transmission (Mansvelder et al., 2002).

1.1.4 Glutamatergic System and Nicotine

Nicotine's effects are also thought to be mediated by enhanced excitatory glutamatergic transmission (Ernhardt et al., 2002; Schilstrom, Nomikos, Nisell, Hertel, & Svensson, 1998) as nicotine acted on VTA nAChRs to increase glutamate release which subsequently activated DA release in the NAcc (Gray et al., 1996; McGehee, et al.,

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1995). Systemic nicotine increased extracellular glutamate and aspartate in the VTA and this was attenuated by VTA administration of an α7 nAChR antagonist (Schilstrom et al., 2000). Blockade of N-methyl-D-aspartate (NMDA) glutamate receptors in the VTA results in attenuation of nicotine-induced accumbal DA increases (Schilstrom et al., 1998). Nicotine also increases glutamate release in the PFC of rodents which may be important in modulating attention as the PFC has been associated with attentional processes (Lambe, Picciotto, & Aghajanian, 2003). Lesioning of the medial PFC, a major source of excitatory VTA innervation, has been shown to reduce α-bugarotoxin (a nicotinic ACh antagonist) binding in the VTA, suggesting that nicotine increases extracellular excitatory amino acids such as glutamate in the VTA via stimulation of nAChRs in the VTA (Schilstrom et al., 2000).

It is quite likely that the independent and interacting functions of the GABA and glutamate systems contribute to the development of smoking. It is the differential desensitization of nAChRs following chronic nicotine exposure between GABAergic and glutamatergic neurons is thought to result in a net excitation, with nAChRs expressed on glutamatergic neurons being less desensitized than those on GABAergic neurons (Mansvelder et al., 2002).

1.1.5. Serotonergic System and Nicotine

It has been speculated that the serotonergic (5-HT) system may be involved in nicotine's rewarding effects (Watkins, Koob, & Markou, 2000); however, evidence for this is primarily indirect. Neuroanatomical studies have found that serotonergic neurons originating in the raphe nuclei innervate both the VTA and the NAcc (Steinbusch, 1981). The findings that 5-HT1A or 5-HT2 receptor agonists differentially influence the

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rewarding properties of nicotine (Olausson, Akesson, Engel, & Soderpalm, 2001), suggests that 5-HT modulation of DAergic neurons may mediate nicotine's effects. Nicotine appears to alter 5-HT release and neuronal activity (Li, Rainnie, McCarley, & Greene, 1998) and acute high doses of nicotine administered systemically, increased 5-HT release in the rat frontal cortex (Ribeiro, Bettiker, Bogdanov & Wurtman, 1993), however, since these doses far exceeded the normal dose of nicotine ingested by a smoker, it's unclear how relevant this finding is. In contrast, application of a selective 5-HT3 antagonist (Corrigall, & Coen, 1994) or a 5-HT1A agonist (Mosner, Kuhlman, Roehm, & Vogel, 1997) had no effect on nicotine consumption, suggesting that there is no role for the serotonergic system in nicotine use. Overall, support for the involvement of the serotonergic system, although contradictory, suggests that it may be involved in nicotine's effects, however, it is unknown to what extent and exactly how serotonergic function is implicated.

1.1.6. Monoamine Oxidase System and Nicotine

Monoamine oxidase (MAO), an enzyme involved in the metabolism of monoamines (including DA, 5-HT and noradrenaline) may function to modulate nicotine's actions, as alterations in MAO availability have consequences in DA availability. Consistent with this, MAO-A concentration in the brains of smokers has been found to be significantly lower relative to non-smokers (Fowler et al., 1998, 1996b) and relative to nonsmokers and ex-smokers, smokers displayed significantly reduced MAO-B as evidenced by PET studies (Fowler et al, 1998, 1996a), indicating that reduced MAO is likely not an antecedent condition. Furthermore, acute nicotine administration did not reduce MAO-B in nonsmokers, thus changes in smokers probably occur gradually

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(Fowler et al., 1999). It is possible that some of the rewarding or aversive effects of nicotine are due to attenuated MAO activity.

1.1.7. Neuroimaging and Nicotine

Single photon emission tomography (SPET) has indicated that acute smoking decreases global cerebral blood flow (Yamamoto et al., 2003), however, following overnight abstinence, PET findings indicated that nicotine increased regional blood flow to some regions while decreasing it in others (Zubieta et al., 2001), with the increases being associated with regions known to have higher densities of nAChRs (Domino et al., 2000a). PET studies have indicated that nicotine increases regional brain flow in smokers, particularly in the thalamus, pons, visual cortex and cerebellum (Domino, et al., 2000a). Consistent with rat findings (Marenco, Bernstein, Cumming, & Clarke, 2000), regional glucose metabolism was found to increase with acute nicotine in smokers, indicating increased activity in a number of brain regions, including the left inferior frontal gyrus, the left posterior cingulate gyrus, the right thalamus and the left and right cuneus of the occipital cortex (Domino et al., 2000b). Acute (i.v.) nicotine administration increased blood oxygenation level dependent (BOLD) contrast signal (a functional magnetic resonance imaging [fMRI] measure thought to indicate cerebral blood flow increases) in the NAcc, cingulate, amygdala, and thalamus (Stein et al., 1998). In contrast, Stapleton et al. (1993) found that whole brain glucose metabolism was reduced with nicotine. Visual smoking cues were found to increase (fMRI) activation in the PFC and midbrain of nicotine-deprived smokers compared to non-smokers (Due, Huettel, Hall, & Rubin, 2002), while nicotine dependent rats, when challenged with mecamylamine, evidenced significant increases in fMRI BOLD contrast in the NAcc

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(Shoaib, Lowe, & Williams, 2004), signifying increased neurotransmission in these areas. A recent review of the current imaging literature concluded that the most common findings in nicotine's effects on smokers implicated relative increases in activation in multiple brain areas including the PFC, inferior frontal, medial frontal and orbitofrontal gyrus, thalamus and visual cortex, some of which are thought to mediate visuospatial attentional processing and withdrawal symptoms (Brody, 2006).

1.2. Individual Differences in Smoking

Although it is clear that many individuals experiment with drugs, including nicotine, only a minority become regular users or become dependent, thus individual differences are thought to play a critical role in determining who will become addicted (Russell, 1989). Individual variation may affect vulnerability to smoking initiation, as increased sensitivity to both the rewarding and the aversive effects of nicotine may lead an individual to develop nicotine dependence, with the individual continuing to use nicotine to avoid withdrawal symptoms (Pomerleau, Collins, Shiffman & Pomerleau, 1993). These sources of variation may include genetic, personality (Gilbert, & Gilbert, 1995), and environmental (Swan, 1999) variables which together may predispose an individual to initiation, maintenance, cessation of smoking and/or other smoking behaviours. The probability that an individual will engage in and continue smoking is thought to be a function of these interrelated factors. It has been argued that the value of elucidating individual differences in susceptibility lies in the fact that it improves the definition of the substance use phenotype which subsequently minimizes biased estimates of contributing factors (Heath, Meyer, Eaves, & Martin, 1991).

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It is clear that genetic variability plays a critical role in individual differences in smoking as nicotine dependence has been found to be heritable (Li, 2006). An individual's initial sensitivity to nicotine was found to be partly genetically determined, with individual differences in genetic factors accounting for 39% of variability in the initiation of smoking (Koopmans, Slutske, Heath, Neale, & Boomsma, 1999). Furthermore, multiple candidate genes have been implicated in susceptibility to nicotine dependence (Munafo et al., 2004). Thus it is clear that the elucidation and characterization of these genetic influences is critical to further exploration of nicotine dependence and smoking behaviours.

Sex differences introduce another source of individual variability, differentiating females and males with respect to nicotine dependence. Numerous studies have evidenced this as females are: less likely to be heavy smokers (Glovino et al., 1994); prefer lower nicotine yield cigarettes (Joonsens & Sasco, 1999); are less nicotine dependent (Bjornson et al., 1995); exhibit reduced plasma cotinine (a nicotine metabolite) concentrations (Ward, Klesges, Zbikowski, Bliss, & Garvey, 1997); in some cases have been shown to have greater difficulty quitting (Escobedo, & Peddicord, 1996; Pirie, Murray, & Luepher, 1991); experience increased withdrawal symptoms (Hatsukami, Skoog, Allen, & Bliss, 1995); and are have a lower rate of cessation and greater relapse rate with nicotine replacement therapy (Wetter, Fiore, Young, McClure, de Moor, & Baker, 1999). It is argued that females and males differ in terms of pharmacological and psychobiological processes related to nicotine use (Benowitz, & Hatsukami, 1998; Grunberg, Winders, & Wewers, 1991; Perkins, 1996; Perkins, Donny, & Caggiula,

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1999). Thus, it is essential that sex differences be considered when examining the acute or chronic effect of nicotine.

Individual differences in environmental and personality factors also contribute to smoking behaviour as both peer and parental influences have been found to influence initiation of smoking (Conrad, Flay, & Hill, 1992; Bailey, Ennett, & Ringwalt, 1993) and shared environment has been found to account for 30% (True et al., 1997) to 54% (Koopmans et al., 1999) of the variability in smoking initiation. Variations in nervous system function have been proposed to underlie trait differences in neuroticism, social alienation (Gilbert & Gilbert, 1995), impulsivity and sensation/novelty-seeking behaviours (Howard, Kivlahan, & Walker, 1997; Mitchell, 1999; Perkins, Gerlach, Broge, Grobe, & Wilson, 2000), which have been identified as risk factors for nicotine addiction.

While it is evident that smoking motivation is multifactorial in nature, there is little clarity as to who becomes addicted and why. It is generally accepted that dependence is initiated with exposure to the drug and subsequent neuroadaptations which lead to a cycle of gradually increased tolerance and increased self-administration (Alexander & Hadaway, 1982). Strong craving and withdrawal symptoms accompany the disruption of this cycle, increasing the probability that smoking behaviour is maintained (Pomerleau, 1995). Two theories of tolerance have been proposed, the exposure model and the sensitivity model. In the former, it is suggested that individuals with a high sensitivity to the aversive effects of nicotine are less likely to experience the repeated exposure necessary to develop dependence (Silverstein et al., 1982). Whereas those with a low sensitivity are more likely to continue to self-administer, leading to the

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development of tolerance and ultimately, dependence (Pomerleau et al., 1993), however, there is minimal empirical evidence to support this contention (Pomerleau, 1995). The sensitivity model posits that a high sensitivity to both the rewarding and aversive effects of nicotine, coupled with repeated exposure, results in the development of selective tolerance to the aversive effects (but not the rewarding effects), and leads to increased nicotine use and the onset of dependence (Pomerleau et al., 1993).

Initial sensitivity to nicotine has been associated with the number of nicotinic receptors and upregulation of nicotinic receptors, which itself is under genetic control, with certain polymorphisms being associated with higher risk of dependence (Collins, & Marks, 1991). It is important to distinguish between a simple genetic predisposition to initiate smoking and the inheritance of variations in structure and biochemistry of the nervous system which result in individual differences in behavioural, affective and cognitive dispositions (e.g. sensitivity) to certain types of appetitive and/or aversive stimuli (Zuckerman, 1992), and may collectively increase or decrease the likelihood that an individual will engage in smoking and develop dependence.

1.3. Heritability of Smoking

Environmental factors contribute to the onset of smoking (Bailey, Ennett & Ringwald, 1993; Han, McGue, & Iacono, 1999), and although twin studies confirm the influence of environment (Heath & Madden, 1995), converging literature suggests substantial heritability of nicotine dependence (Li, 2006), sensitivity to nicotine (Marks, Stitzel, Collins, 1989), age of onset, number of cigarettes smoked per day (Koopmans et al., 1999), initiation, persistence, and degree of dependence (Madden et al., 1999; True et al., 1997). In twin studies, concordance rates for smokers were higher in monozygotic

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twins than in dizygotic twins, with heritability estimates ranging from 28 to 84% (Hughes, 1986). Heritability estimates of 75%, 80% and 60% have been established for initiation, regular use, and nicotine dependence respectively, with over 80% of the variance in susceptibility to initiation and regular use being shared (Maes et al., 2004). Consistent with this, a recent meta-analysis of 17 twin studies found an overall heritability estimate for dependence of 56%, with gender mediating the degree of heritability (females 46%, males 59%) (Li, 2006).

The genetic contribution to smoking behaviour is also supported by the implication of numerous candidate genes, including DRD2, DAT, 5-HTT, CYP2A6 (Munafò, Clark, Moore, Payne, Walton, & Flint, 2003), DRD4, DRD1 (Young, Lawford, Nutting, & Noble, 2004), and catechol-O-methyltransferase (COMT) (Beuten, Payne, Ma, & Li, 2006). In a meta-analysis of 28 association studies, the DRD2 Taq1A polymorphism has been related to smoking initiation, and the 5-HTT LPR and CYP2A6 reduced activity polymorphisms were related to both smoking cessation and to cigarette consumption (Munafò et al., 2004). An association study has suggested that the Val/Met variant of the COMT gene has a role in nicotine dependence (Beuten et al., 2006), and the DRD4 L allele has been found to confer susceptibility to nicotine dependence in an African (but not Caucasian) population (Shields et al., 1998).

It has been suggested that neurotransmitter function as modulated by genetic influences represents one the fundamental elements underlying substance abuse (Young, et al., 2004). Many of the candidate genes that have been suggested to underlie some of nicotine's effects have implicated the midbrain dopaminergic pathway, which is consistent with its involvement in the rewarding properties of many substances of abuse.

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The DA receptors have been examined with interest in their involvement in nicotine dependence and in particular, the DRD2 polymorphism has been the subject of much study as the finding of reduced midbrain D2 receptors density provides support for the reward deficiency syndrome (Blum et al., 2000) which posits that substance abuse often functions to elevate DA levels, compensating for chronically low levels of this neurotransmitter. Thus DRD2 represents an ideal candidate gene for further investigation.

1.4. DRD2 and Nicotine

The Taq1 polymorphism of the DRD2 gene is a restriction fragment length polymorphism (RFLP), located on chromosome 11 at q22-q23 (Grandy et al., 1989), in the 3' untranslated region (UTR) of the gene approximately 9.5kb downstream of the DRD2 gene (Grandy, Zhang, & Civelli, 1993) with two known alleles, identified as A1 and A2. The mechanism by which this variant exerts its effects on the DRD2 gene is unclear, however, a single nucleotide polymorphism (SNP) in a protein kinase gene, which itself appears to be unrelated to addiction, may play a role (Neville, Johnstone, & Walton, 2004). It is possible that it may exert its effects either via linkage disequilibrium with another functional DRD2 variant or by being in a yet to be determined regulatory or coding region (Reuter et al., 2005). The presence of the less common A1 allele has been associated with attenuated dopamine receptor availability in the striatum (Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991; Thompson, et al., 1997), lower glucose metabolism in dopaminergic areas (Noble, Gottschalk, Gallon, Ritchie & Wu, 1997), and reduced dopamine D2 receptor density (Jönsson, et al., 1999; Pohjalainen, et al., 1998), implicating the DRD2 gene in the midbrain reward circuitry.

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The precise relationship between the DRD2 variant and smoking has yet to be elucidated, however, there is support for the existence of the relationship. Dopaminergic hypofunction, which is associated with the A1 allele, is postulated to mediate vulnerability to smoking dependence (Comings et al., 1996; Gilbert, & Gilbert, 1995; Noble et al., 1994b). Consistent with this proposition, a higher prevalence of the A1 allele has been documented in smokers compared to nonsmokers (Comings et al., 1996; Noble, 2003; Noble, et al., 1994b; Spitz et al., 1998), and in multi-substance abusers relative to controls (Smith, et al., 1992), and although not all studies have noted differences between smokers and nonsmokers with respect to the frequency of the A1 allele (Singleton et al., 1998), the incidence of the A1 allele has been shown to increase progressively from nonsmokers to ex-smokers to smokers (Noble et al., 1994b). The A1 allele has also been linked to higher incidence of drug abuse in general, including nicotine use, relative to the A2 allele (Noble, 2000; Young, Lawford, Nutting, & Noble, 2004). Presence of the A1 allele has been found to increase susceptibility to smoking initiation, result in poorer treatment outcomes (Munafo, Clark, Johnstone, Murphy & Walton, 2004), increase the number of cigarettes smoked (Waldman, Robinson, & Rhee, 1999), result in stronger cue induced craving (Erblich, Lerman, Self, Diaz, & Bovbjerg, 2005), lead to nicotine dependence (Comings, et al., 1996; Noble et al., 1994b), and lead to increased vulnerability to dependence (Comings et al., 1994). Individuals with the A1 allele were also reported to be less likely to successfully quit smoking (Cinciripini et al., 2004), although this was not supported by Berlin, Covey, Jiang, & Hamer (2005). In general these findings suggest a role for the DRD2 genotype in nicotine dependence.

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1.5. Endophenotypes

Concepts such as cognition and drug dependence/addiction represent phenotypes, or the observable expression of a given genotype(s). However, these phenotypes are sufficiently broad, complex, and multifactorial (i.e., represent the cumulative effect of multiple genotypes, among other factors) in origin and expression as to evade clear definition and as such, accurate and reliable assessment of contributing genetic factors is precluded. Gottesman and Gould (2003) have suggested that the lack of biological markers and anatomical variants combined with the generally subjective measures used for clinical diagnosis interferes with the a clear definition of the subject of interest and without a clear operational definition, it is unclear exactly what is being measured and thus, comparison between studies is limited (Bearden & Freimer, 2006). A recent trend toward the use of intermediate phenotypes (endophenotypes) has attempted to address these difficulties.

Defined originally as an internal phenotype that lies intermediate between the gene and the disease itself (Gottesman & Shields, 1973), the concept of an endophenotype has more recently been defined as a quantitative trait thought to be an intermediate between disease phenotypes and the biological processes that underlie them, with the assumption being that the endophenotype represents more elementary phenomena than those involved in complex diagnoses or functions (Bearden & Fremier, 2006; Gould & Gottesman, 2006), is presumably under the control of fewer genes (Gottesman & Gould, 2003), and thus the genetic contributions can be more readily examined. However, a recent review and meta-analysis of endophenotype use suggests that while their usefulness is evident, it is important to note the possible limitation that

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their genetic basis may be as complex as that of the larger concept (Flint & Munafo, 2007). Equally relevant is the suggestion that while the endophenotype may reduce complexity, it does not eliminate complexity as contributions from the environment, individual differences, and numerous other sources must still be considered.

An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological in nature (Gottesman, Gould, 2003). Although still debated, there is some agreement as to the necessary and sufficient criteria used to qualify an endophenotype. Primary among these criteria is that the endophenotype must: exhibit moderate heritability; display stability, reliability, and validity; be associated with causes, with the net effects of disorder be more frequent in unaffected family of an affected individual relative to the population and; vary continuously in the general population (Bearden & Fremier, 2006).

Measures of cognitive function, such as attention, are widely accepted endophenotypes as they are reliable and stable over time (Rund, 1998) and the use of endophenotypes has been demonstrated in a number of studies of psychiatric disorders, although often with the endophenotype not meeting all of the criteria (Gottesman & Gould, 2003). An endophenotype is presumed to be more directly linked to genotype than a more broadly defined and complex phenotypes such as cognition (Gottesman, & Gould, 2003; Iacono, Carlson, & Malone, 2000), thus event-related potentials (ERPs), and in particular, the attention-sensitive P300 component of the event-related brain potential (Yoon, Iacoco, Malone, & McGue, 2006), as well as behavioural performance measures (Braff & Light, 2005) have been proposed as useful endophenotypes in psychiatric disorders. As measures of sustained attention (versus other forms of

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attention) have reliably been employed to examine nicotine-induced attentional changes, it may represent a good candidate paradigm in which to examine the proposed endophenotypes.

Although the P300 does not meet all of the criteria for an endophenotype, it is heritable, and has been used in alcoholism to determine genetic risk, it has provided information about clinical sub-grouping, the disease process and therapeutic response (Enoch, Schuckit, Johnson, & Goldman, 2003; Hesselbrock, Begleiter, Porjesz, O'Connor, & Bauer, 2001; Yoon et al., 2006). Ample evidence from family and twin studies suggest that the P300 amplitude is heritable, as heritability estimates have been found to range from 39 to 79% (Almasy et al., 1999; O'Connor, Morzorati, Christian, & Li, 1994; Wright et al., 2001). In addition, P300 amplitude has been found to be reduced in preadolescent boys of alcoholic fathers, relative to boys with no familial substance abuse history (Polich, Pollock, & Bloom, 1994). Reduced P300 amplitudes have been implicated in multiple substance use disorders, including cocaine and heroin addiction (Bauer, 2001; Biggins, MacKay, Clark, & Fein, 1997), nicotine (Anokhin et al., 2000; Polich & Ochoa, 2004), and long-term cannabis use (Solowij, Michie, & Fox, 1991), suggesting that it represents a good candidate endophenotype for substance abuse in general (Yoon, et al., 2006). In addition, the application of multivariate endophenotypes has been advocated as this may provide enhanced between group discriminatory power (Iacono, Carleson & Malone, 2000) and as such, the combined use of P300 amplitude response and behavioural performance measures as endophenotypes is supported. Since the DRD2 genotype has been found to impact behavioural performance, with nicotine facilitating performance more in individuals with at least one A1 allele (Gilbert, 2005), it

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is reasonable to employ attention-dependent P300 performance endophenotypes when examining the relationship of DRD2 polymorphisms to acute pharmacological response to nicotine.

1.6. Event-related Potentials

ERPs are event-locked (internal or external) electrical potentials extracted from the scalp-recorded electroencephalogram (EEG) by filtering and signal averaging (Picton et al., 2000). A number of these ERP components associated with distinct behavioural processes have been characterized, with the identification of the various ERP components being conventionally based on voltage polarity (positive [P] or negative [N]), topographic distribution and latency (Hugdahl, 1995). ERP component nomenclature is descriptive in that it often reflects these three features. Although limited in spatial resolution, ERPs provide a noninvasive means to measure/assess brain activity with millisecond temporal resolution that is superior to other functional imaging strategies, including MRI and PET (Fabiani, Gratton & Coles, 2000). This makes it possible to assess when and to a lesser extent, where processing is taking place in the brain (Picton et al., 2000). The components are thought to reflect underlying neural activity and can be used to differentiate different cognitive conditions (Coull, 1998). ERPs are typically characterized as being either 'exogenous' or 'endogenous' (Fabiani, Gratton & Coles, 2000; Picton et al, 2000). The former, exogenous components, which are early (<100ms) components, have amplitudes and latencies which are driven by the physical characteristics of stimuli (e.g., modality, intensity, frequency) (Picton et al, 2000), while the latter components are later (100-1000ms) and have amplitudes and latencies which

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are related not to the stimulus features per se, but to their significance and the manner in which they are processed (Loveless, 1983).

The P300, an endogenous positive ERP, occurs in response to a stimulus to which the subject is actively attending, and is particularly pronounced if the stimulus is infrequent or unexpected (Sutton, 1965). Two subcomponents are typically identified, the P300b and the P300a. The former is a late positive voltage deflection, located 250-500 ms post stimulus onset and is approximately 10 μV in amplitude relative to the prestimulus baseline with a centroparietal maximum in response to target detection while the P300a has a frontal maximum, and is elicited involuntarily by novel stimuli (Picton, et al, 2000). For the purposes of this paper, P300 will be used to indicate P300b. The P300 is most commonly elicited within the auditory 'oddball' paradigm, a simple discrimination task in which rare target stimuli are randomly embedded within a series of standard (frequently occurring) stimuli and participants are required to attend and respond to the target either mentally (counting) or behaviourally (button press).

The context-updating hypothesis suggests that P300 amplitude is a metric of brain activity when the mental representation of the stimulus environment is updated (Donchin, 1981). It is the comparison of a stimulus to that which precedes it that purportedly generates the P300, but it occurs only when a difference exists that attentional resources are engaged and subsequently, the memory representation for the stimulus is updated (Donchin et al, 1986). Several factors relating to stimulus characteristics influence the P300, including probability and ease of discrimination of target stimuli (Johnson, 1986), with P300 amplitude being increased with improbability of the target and reduced in cases where the target is not readily distinguishable from the non-target stimuli.

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The latency of the P300 is an index of stimulus classification speed and is independent of response selection and thus of response time (Polich, 1998). That latency is not related to response selection is evident, as latency is not affected when response-related processing speed is influenced (Donchin, 1981). P300 latency is however affected (lengthened) by increased stimulus complexity which results in greater difficulty of classification (Cacioppo, & Tassinary, 1990). As P300 latency is unaffected by response selection or time, it is thought to be a sensitive temporal measure of the neural activity underlying attentional allocation (Polich, 1998). The P300 latency is also negatively correlated with cognitive function in healthy subjects (Emmerson, Dustman, Shearer, & Turner, 1989).

Heritability of the P300 (one of the criterion of an endophenotype), and in particular, heritability of P300 latency is supported by twin studies, with monozygotic twins (MZ) displaying greater similarity than unrelated controls (Polich & Burns, 1987; Surwillo, 1980) and within twin variability being reduced in MZ compared to dizygotic (DZ) twins (Rogers & Deary, 1991). A heritability 0.60 has been estimated for the P300 amplitude and 0.51 for the P300 latency (van Beijsterveldt & van Baal, 2002), while a more recent estimate for P300 amplitude has indicated a heritability of 0.69 (Hall et al., 2006).

The dopaminergic system has been implicated in the attentional and reinforcing properties of nicotine (Corrigall, Franklin, Coen, & Clarke, 1992) and the P300 (index of attention) has been found to be associated with the dopaminergic system, as latency is prolonged in Parkinson's disease (which is characterized by widespread loss of DA fibres), but this is reversed with the administration of L-dopa (Stanzione et al., 1991). A

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relationship between DRD2 and the P300 is evident in the administration of a DRD2 antagonist which has been shown to prolong latency (Stanzione et al., 1990). Post-mortem analysis of aged brains revealed a reduction in DRD2 (Seeman et al., 1987) and prolonged P300 latency is a characteristic of aging (Picton, et al 1984). The dopaminergic system may modulate the P300 in a genotype-dependent manner as the presence of the DRD2 A1 allele results in significantly longer latencies relative to the A2 allele (Noble, Berman, Ozkarogoz, & Ritchie, 1994a), however, this was not replicated by Lin, Yu, Chen, Tsa, and Hong (2001), who suggest that the relationship may be disease dependent. Despite some contradictory results, the P300 represents a reasonable candidate as an endophenotype mediating the DRD2 genotype-dependent attentional effects.

1.7. Attention and Nicotine

Although not easily defined, attention has been characterized as a heterogeneous phenomenon involving the appropriate allocation of processing resources to relevant stimuli, with a number of processes subsumed under the broad label of attention (Coull, 1998). Various forms of attention have been identified: attentional orientation (ability to direct attention toward stimuli); selective attention (attending to one stimulus type over another); divided attention (simultaneous attending to more than one stimulus), and; sustained attention (continued attending to one stimulus over time) (Coull, 1998). It is this latter form of attention that is most consistently affected by nicotine as evidenced by the enhancement of focused attention (Heishman, Taylor, & Henningfield, 1994), and sustained focused attention (Evenden, Turpin, Oliver, & Jennings, 1993; Lindgren, Stenberg, & Rosen, 1998; Mancuso, Andres, Ansseau, & Tirelli 1999; Mirza &

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Stolerman, 1998), while selective and divided attention have not been shown to be consistently affected by nicotine (Heishman, et al., 1994; Mancuso et al., 1999; Rusted, Caulfield, King, & Goode, 2000).

Information processing within cognitive domains (e.g., attention, working memory) involves the activation of distinct distributed brain networks as evidenced by neuroimaging studies. In smokers, nicotine increased frontal activation during attentional tasks (Lawrence, Ross, Stein, 2002), while in non-smokers, nicotine, relative to placebo, activated frontal and parietal areas in a working memory task as evidenced by BOLD fMRI (Kumari et al., 2003; Lawrence, Ross, & Stein, 2002). Furthermore, brain imaging studies indicate that i.v. nicotine selectively increases regional cerebral blood flow in parieto-occipital regions in smokers and nonsmokers (Ghatan et al., 1998) and cortical and subcortical limbic areas in nondeprived smokers (Stein et al., 1998). Together, these results suggest that attention activates widespread and distinct brain regions and that the regions activated depend in part on nicotine dependence.

With respect to different forms of attention, the literature suggests that while similarities exist in their activation profiles, they are also engaging different neural pathways. PET studies have indicated that tasks recruiting selective attention activate the anterior cingulate (Bench et al., 1993; Pardo, Pardo, Janer, & Raichle, 1990) and possibly the frontal cortex (Corbetta, Miezin, Shulman, & Petersen, 1993). Similarly, increased activity is evident in the right PFC and anterior cingulate during divided attention tasks (Corbetta Miezin, Dobmeyer, Shulman, & Petersen, 1991). Sustained attention has been shown to activate frontal and parietal cortices (especially in the right hemisphere) (Pardo, Fox, & Raichle, 1991) and also activates the thalamus (Coull, Frackowiak, & Frith, 1998;

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Kinomura, Larsson, Gulyas, & Roland, 1996). Coull (1998) demonstrated that the rapid visual information processing (RVIP) task of sustained attention activated frontal, parietal and occipital cortices, regions that have been implicated in attentional processes by other imaging (Cabeza & Nyberg, 2000) and lesion studies (Rueckert & Grafman, 1996, 1998). Furthermore, the ascending cholinergic system originating in the basal forebrain and projecting to most of the cortex has been found to be critical for sustaining attention (Everitt & Robbins, 1997; Muir, Everitt, & Robbins, 1995).

Performance on a variety of cognitive functions may be improved with nicotine, as is evident in both human and animal models. Nicotine has been shown to have beneficial effects on performance in attention and memory tasks (Rezvani & Levin, 2001), with nicotine improving word recall (but only with effortful processing) (Rusted, Graupner, Tennant, & Warburton, 1998) and enhancing sustained attention, recognition memory and reasoning abilities (Bell, Taylor, Singleton, Henningfield & Heishman, 1999) in smokers. In addition, nicotine has been shown to improve accuracy in non-smokers in a working memory task (Kumari et al., 2003). Nicotine has also been shown to enhance attentional functions in both smokers and non-smokers (Foulds et al., 1996; Levin, et al., 1998) and it has been suggested that nicotine exerts its effects by focusing attention and increasing resource capacity in both smokers and nonsmokers (Ernst, Heishman, Spurgeon, & London, 2001), which is consistent with the contention that nicotine optimizes, rather than improves attention as nonsmokers with low, (but not high) attention evidenced fewer errors in a sustained attention task (Poltavski & Petros, 2006), however the underlying mechanisms are not understood.

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The RVIP task, a paradigm that putatively engages sustained attention, has been employed frequently to examine nicotine's performance enhancing effects (Wesnes, & Warburton, 1983). Smokers exhibited increased performance in the RVIP task subsequent to acute nicotine administration (Parrott, & Craig, 1992), with both transdermal nicotine (Warburton & Mancuso, 1998) and smoking (Warburton, & Arnall, 1994; Wesnes, & Warburton, 1983) increasing reaction times and improving accuracy in this task. Acute nicotine has enhanced attentional function in both smokers and non-smokers (Foulds et al., 1996; Levin et al., 1998), as evidenced by decreased reaction times (Bekker, Bocker, Hunsel, van den Berg, & Kenemans, 2005; Levin et al., 1998), and decreased variability in reaction times (Levin et al., 1998). In some studies (Bekker et al., 2005; Levin et al., 1998; White & Levin, 1999), but not all (Pritchard, Sokhadze, & Houlihan, 2004), an improvement in both response accuracy and omissions has been observed with nicotine. Findings in non-smokers, however, have been inconsistent, with some indicating no association between attention and nicotine administration (Klepkamp, Jennings, Blank, & Eissenberg, 2005), while others support improved attention (Levin, Simon, & Connors, 2000, as cited in Levin, McClernon, & Rezvani, 2006).

Animal studies, paralleling the findings of human studies, have consistently supported the putative attention-augmenting properties of nicotine. In tests of attention, nicotine enhanced response accuracy (Grilly, 2000; Hahn, Shoaib, & Stolerman, 2002; Hahn & Stolerman, 2002), reduced omission errors (Hahn, Shoaib, & Stolerman, 2002; Hahn & Stolerman, 2002), decreased reaction times (Blondel, Sanger, & Moser, 2000; Grilly, 2000; Grottick & Higgins, 2000; Hahn, Shoaib, & Stolerman, 2002; Hahn & Stolerman, 2002), while mecamylamine induced a modest decrement in reaction time

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only (Stolerman, Mizra, Hahn, & Shoaib, 2000) in rodents. These effects of nicotine appear to be dose-dependent, with small doses increasing the number of correct detections, decreasing the number of omission errors, decreasing reaction times (Mizra, & Bright, 2001; Stolerman et al., 2000) and increasing correct rejections (Rezvani, Bushnell, & Levin, 2002). The attentional enhancements are thought to be further modulated by other factors as the strain of rat utilized has been shown to affect response to nicotine (Mizra & Bright, 2001).

Impairments in attention and other cognitive functions have been observed within twelve hours of smoking cessation (Bell et al., 1999) and this deficit is ameliorated with nicotine administration (Bell et al, 1999; Heishman, et al., 1994). For example, deprived smokers evidenced prolonged response latencies on the Sternberg task of selective attention and nicotine reversed this increase in latency (Havermans, Debaere, Smulders, Wiers, & Jansen, 2003) and this may illustrate a relief from withdrawal rather than an actual improvement in attention (Heishman et al 1994; Hughes, 1991). It has been proposed that nicotine's effects are confounded by degree of withdrawal in smokers and smoking status (Ernst et al., 2001; File, Dinnis, Heard, Irvine, 2002; Heishman, 1998). However, studies with non-smokers suggest that a simple relief from withdrawal is not supported as nicotine improved attention in this population using either RVIP tasks (Wesnes, & Warburton, 1984; Foulds et al., 1996) or continuous processing task (CPT) paradigms (Levin et al., 1998).

1.8. Dopamine and Attention

That nicotine has demonstrated effects on attention implicates the cholinergic system, however evidence also points to the involvement of DAergic systems. This is

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evidenced by the fact that: nigrostriatal DA lesions induced inattention syndrome in baboons (Viallet et al., 1984); rats with unilateral DA depletion lesions in striatum displayed increased response time to shift visuospatial attention (Ward & Brown, 1996), and; mesencephalic dopaminergic lesions resulted in attentional deficits as evidenced by the fact that animals had difficulty switching from one situation to another in a five choice test (Baunez & Robbins, 1999). Low doses of the DA antagonist, haloperidol, but not scopolamine, disrupted performance on sustained attention tasks in rats and attenuated amphetamine (DA agonist) induced attentional disruption, suggesting DA involvements in attentional processing (Brockel & Fowler, 1995). DRD2 blockade impaired attention in normal humans (Clark et al., 1986, 1987a,b) and in rats (neuroleptically treated) on a CPT analogous task (Skjoldager & Fowler, 1991). Furthermore, in patients with Parkinson's disease (characterized by marked depletion of striatal DAergic neurons), ERP studies suggest that the DAergic system contributes to voluntary and sustained control of visuospatial attention, and response preparation, while automatic control of visuospatial attention is independent of the DAergic system (Yamaguchi & Kobayashi, 1998).

A review of the literature on dopamine and attention has suggested that basal ganglia and frontal lobe structures are primarily implicated in cognitive deficits (as opposed to generalized DAergic deficits) and further suggested that a correlation exists between DA innervation and cognitive/attentional capacity (Nieoullon, 2002). More recently, Nieoullon & Coquerel (2003) suggest that DAergic activation may be implicated in novelty detection. Thus, the DAergic system appears to be implicated in

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attention, likely as a neuromodulator (Seamans, & Yang, 2004), however the precise circuitry and mechanisms by which dopamine mediates attention has yet to be elucidated.

Event related potential measures have been employed in attentional assessment as a useful adjunct to the standard performance measures (reaction time and frequency of errors) as it is suggested that performance measures are limited in that they represent a single measure, with multiple underlying processes (Pritchard, Sokhadze, & Houlihan, 2004). Furthermore, it has been suggested that ERPs may be more sensitive to detection of nicotine's effects than behavioural reaction time measures, however the authors argue for the use of both measures to provide more clarity with respect to interpretation of results (Pritchard, Sokhadze, & Houlihan, 2004). The P300 in particular has been successfully used to index nicotine-induced changes in attention. Attenuated P300 amplitudes (but not latencies) were observed in smokers, relative to non-smokers (Anokhin et al., 2000). P300 amplitudes were found to increase with the administration of transdermal nicotine (Knott, Bosman, Mahoney, Ilivitsky & Quirt, 1999) and with smoking, amplitudes increased and latencies decreased (Houlihan, Pritchard, & Robinson, 1996, 2002; Knott, Kerr, Hooper, & Lusk-Mikkelsen, 1995). However, no differences were observed between smokers and non-smokers on P300 measures following acute nicotine administration (Ascioglu, Dolu, Golgeli, Suer, & Ozesmi, 2004).

With respect to the relationship between the P300 and reaction time, nicotine appears to exert differential effects dependent on stimulus modality. Although controversial, the bulk of evidence suggests that in the visual modality (Hasenfratz, Michel, Nil, & Battig, 1989; Knott, Bosman, Mahoney, Ilivitsky, & Quirt, 1999), P300 amplitude and reaction time covary with nicotine administration, whereas, in the auditory

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modality only a few studies support this relationship. A review of the literature suggested that if nicotine does increase speed of visual processing, it does so by increasing the availability of attentional resources, while in auditory processing nicotine may exert effects, but via mechanisms other than altered attentional resources (Pritchard, Sokhadze, & Houlihan, 2004).

Nicotine-induced effects appear to be modulated by task difficulty (Knott et al., 1995; Pritchard & Robinson, 1998; Ilan & Polich, 1999, 2001; Polich & Criado, 2006), and amount smoked (Kodama et al., 1996; Lindgren et al., 1999). Task characteristics also appear to play a modulatory role, as increased P300 amplitudes were only evident in visual (and not auditory) attentional tasks (Houlihan, Pritchard, & Robinson, 1996). With respect to RVIP-elicited P300s, smoking deprivation was found to decrease amplitudes and increase latencies while smoking reversed these effects, with P300 amplitudes and latencies of smoking smokers being similar to that of non-smokers (Knott et al., 1995).

1.9. Summary, Objectives, Hypotheses

Taken together, these findings implicate multiple neurobiological systems and interacting factors in the effects of nicotine and support the use of clearly defined endophenotypes as being critical to the analysis of the mechanisms underlying nicotine use and its effects. As an endophenotype, the P300 and behavioural performance measures of sustained attention show promise in enabling the elucidation of the underpinnings of nicotine dependence. Furthermore, the strong heritable component of nicotine dependence in conjunction with the implication of multiple candidate genes (in particular DRD2) supports the investigation of DRD2 polymorphisms in the attentional effects of acute nicotine administration.

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Although the exact mechanism by which DRD2 A1 allele predisposes to cigarette smoking is not known, it is reasonable to propose the A1 and A2 alleles exert different effects on central processes underlying acute responsiveness to nicotine and non-nicotine rewarding components of acute smoking. The present study was conducted to investigate the possibility that DRD2 genotype modulates nicotine's attention-augmenting properties as assessed with ERP and behavioural performance measures in an RVIP task in healthy non-smokers. Nicotine has demonstrated attention-augmenting and performance-enhancing properties (Rezvani, & Levin, 2001). As carriers of the A1 allele of the DRD2 gene have demonstrated reductions in DRD2 receptor densities in the striatum, and general dopaminergic hypofunction (Jönsson et al., 1999; Pohjalainen et al., 1998) and have evidenced enhanced behavioural performance following nicotine administration (Gilbert et al., 2005), the following primary hypotheses are forwarded:

1) individuals with the A1 allele will exhibit greater attentional benefit with acute nicotine (vs. placebo) administration relative to A2 homozygotes, as indicated by increased P300 amplitudes.
2) individuals with the A1 allele will exhibit greater processing speed with acute nicotine (vs. placebo) administration relative to A2 homozygotes, as indicated by shortened P300 latencies.
3) individuals with the A1 allele will exhibit greater performance benefits with acute nicotine (vs. placebo) administration relative to A2 homozygotes, as evidenced by shortened reaction times, increased target detections, and reduced response errors relative to placebo.

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By utilizing electrophysiological/behavioural-based phenotypes, this research may have important clinical implications in that laboratory assessment of acute responsiveness to nicotine, combined with genotyping, may prove to be a useful early treatment strategy in cessation trials for objective identification who are acutely responsive/non-responsive to nicotine or non-nicotine reinforcement and hence, are more likely to respond to an appropriately tailored pharmacological or non-pharmacological intervention.

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2.0 Method

2.1. Participants

Acknowledging that previous studies (Pohjalainen et al., 1998; Jonsson et al., 1999) have reported (in healthy Caucasians) prevalence rates of 28% and 72% for DRD2-A1 and DRD2-A2 alleles, respectively, an attempt was made to recruit approximately 30 non-smokers from the community to participate in order to achieve the desired sample size. A sample of 29 healthy non-smokers was recruited, however the final sample included 24 participants, with ten (5 female) having the DRD2-A1 (A1/A1 or A1/A2) genotype and fourteen (6 female) being homozygous DRD2-A2 (A2/A2). One participant was lost due to side effects of nicotine, and four others were excluded from final analysis, as genotyping did not succeed for three and the behavioural performance of the fourth fell below the minimum 60% required. The inclusion of only non-smokers was predicated on the fact that: it eliminated a potential confound that would otherwise be introduced by nicotine withdrawal in abstinent smokers, and; this population was more readily accessible than smokers. Recruits were required to undergo an initial telephone screening to establish that they were right-handed, between 18-40 years of age, have smoked a lifetime maximum of 10 cigarettes (none in the past year), and had no past or current history of a significant mental or medical illness, alcohol/drug abuse or current use of medications. A second screening was conducted on the day of the first test session, and involved: self-reports to exclude those with a psychiatric history and/or history of serious physical illness; a saliva sample (for genotyping), and the completion of personality trait questionnaires (including the Eysenck Personality [EPQ] Questionnaire (Eysenck & Eysenck, 1975) and the Sensation Seeking [SSS-V] Scale (Zuckerman, 1994), and a brief intelligence test. Attempts were made to

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match individuals on gender, age. As well, attempts were made to match groups on neuroticism (N), extroversion (E) and psychoticism (P), dimensions of the EPQ and on the Experience Seeking (ES) and Disinhibition (DIS) factors of the SSS.

2.2. Design

Volunteers attended the Clinical Neuroelectrophysiology and Cognitive Research Laboratory at the Royal Ottawa Hospital for two test sessions and were assessed in a randomized, double-blind, placebo-controlled, cross-over design (i.e. within subject comparison of the Nicorette® nicotine gum versus placebo gum) design with 2 parallel treatment groups (DRD2-A1 and DRD2-A2 genotypes). The order of the nicotine and placebo sessions (separated by a minimum of 2 days) was randomized across participants, such that half (randomly selected) were administered nicotine gum in the first session and placebo gum in the second session, while the remaining half received their treatments in the reverse order.

2.3. Procedures

Prior to arriving at their two morning (beginning 8:00 a.m.) test sessions, volunteers were instructed to abstain overnight (beginning at midnight) from food, caffeine, alcohol, drugs, and medications. Following the signing of an informed consent and the verification of abstinence, participants were seated in a comfortable chair in a sound attenuated, electrically shielded room and after a saliva sample (1.5 milliliters) was taken, ERP electrodes were attached. Participants were instructed to sit upright and keep movements, including blinking, to a minimum during the two RVIP/ERP assessments within each session, at baseline and again following the administration of the nicotine or placebo gum. Subsequent to the second recording, participants completed a self-report questionnaire

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regarding adverse events experienced during the gum administration. Within each of the 2 assessment blocks, the following assessments were carried out: a cognitive processing paradigm, involving a 10 minute rapid visual information processing (RVIP) task (a task of sustained attention requiring detection of low-probability [$p = .2$] 3-odd or 3-even numbered [target] digit sequences [randomly presented amongst non-target digits at a rate of 110 digits/min), which has been shown to be sensitive to both withdrawal [Cook et al., 2003] and acute smoking/nicotine [Mancuso, Andres, Anzeau & Tirelli, 1999]; behavioural performance measures were evaluated for response accuracy and speed indices and concomitant ERP recordings were assessed for target-elicited P300 amplitudes and latencies.

2.4. Nicotine

A recent review of nicotine dose selection has advocated the consideration of two factors in determining route of administration: the hypotheses being tested and practical limitations (Matta et al., 2007). Thus, the need to approximate the speed and quantity of nicotine delivery that is associated with inhaled nicotine must be balanced by the invasive or aversive properties associated with the chosen route of administration in the population of interest. The nicotine gum was been chosen as it combined the most rapid peak nicotine levels, with the fewest aversive effects in non-smokers. The acute nicotine treatment consisted of two pieces of Nicorette® gum, a 4mg and a 2mg dose, administered simultaneously, with a maximum plasma nicotine concentration of approximately five ng/mL being achieved in half an hour. The placebo gum was similar in size, texture and taste. Participants were blindfolded when the gum was first administered and wore a nose-plug throughout gum chewing to minimize detection of gum type. Participants were

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instructed by a pre-recorded message to chew the gum twice every minute for thirty minutes. Both participant and investigator were blind to gum randomization.

2.5 Genotyping

Saliva samples underwent extraction of DNA for polymerase chain reaction (PCR) analyses with the commercially available Oragene DNA extraction kit (DNA Genotek). Aliquots of extracted DNA were used in subsequent real time PCR analyses in 5 μL mixtures containing Taqman universal master mix, forward and reverse primers, FAM- and JOE-labelled probes. Following denaturation at 95°C for 10 minutes, DNA was amplified with 45 cycles of 92°C for 15 seconds and 60°C for 60 seconds. Three DRD2 TaqIA genotypes were revealed, with the A2 homozygote generating two restriction fragments, the A1 homozygote generating an uncleaved fragment and the heterozygote generating three restriction fragments. Reliability and validity of results was assessed by comparison with previously characterized standards for DNA samples. Genotyping for the DRD2-TaqI-A polymorphism followed previously used procedures (Lerman et al., 1999; Cinciripini et al., 2004; David et al., 2003) where genotype was characterized by the presence or absence of the DRD2 A1 allele, collapsing the homozygous A1/A1 and heterozygous A1/A2 participants and contrasting them with A2/A2 allele participants (this procedure being consistent with studies showing associations with addictive/compulsive behaviours (Lerman et al., 1999; Cinciripini et al., 2004; David et al., 2003) .

2.6 Measures

In addition to the self-report measures of mood, electrophysiological endpoint measures were acquired with Brainvision and Presentation software and included: RVIP-extracted target-elicited P300 amplitudes/latencies from 32 scalp sites, with primary

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measures being extracted from the three mid-line (F_z, C_z, P_z) sites, and RVIP behavioural performance measures including target detections, false alarms and reaction time in the cognitive processing paradigm. EEG activity was referenced to activity recorded from electrodes placed on left and right tempoparietal sites and a frontocentral site served as the ground. Electrodes placed on the supraorbital ridge and the suborbital ridge of the right eye and on the canthus of both right and left eyes were used to monitor electro-oculographic (EOG) activity and subsequently minimize contamination from eye movements and blinks. Electrode impedances were maintained at less than 5 kΩ for the duration of each session. The EEG and EOG amplifier bandwidth filters were set at 0.1–30 Hz, digitized at 500 Hz and the on-line computerized analog-to-digital sampling rate time-locked to each stimulus presentation were carried out at four millisecond steps for a 1000 ms epoch, beginning 100 ms prior to stimulus onset. Digitized single-stimulus trial epochs were stored to disk and were subsequently processed off-line with four analytical procedures. To reduce effects of non-cerebral (e.g. head movements) and ocular artefact contamination on EEG, the Gratton & Coles algorithm (Gratton, Coles & Donchin, 1983) was employed to correct for eye movements/blinks and corrected single trial epochs with EEG and EOG voltages exceeding ±100μV were eliminated from further analysis. Averages were constructed for each stimulus type (frequent and rare) at each of the three primary recording sites. To reduce the contamination of high frequency electrical activity on waveform component identification and measurement, the averaged ERP waveforms were digitally filtered using the filter bandpass, set at 0.15-8Hz, with slope set at 24dB/octave. P300 components were measured as the largest average peak positive voltage ±5 voltage points around the peak value, within a latency window of 300 to 750

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ms post stimulus onset. P300 latency was derived at P_z, the site of maximal amplitude with the measurement of amplitude at all other sites being in reference to P_z latency. Figure 1. displays a single subject waveform with a clear P300 in to deviant stimuli and none in response to standard stimuli, with P300 amplitude increasing progressively from anterior to posterior.

The behavioural performance measures (reaction time, false alarms, target detections) included only those responses between 100 ms and 1000ms post stimulus onset.

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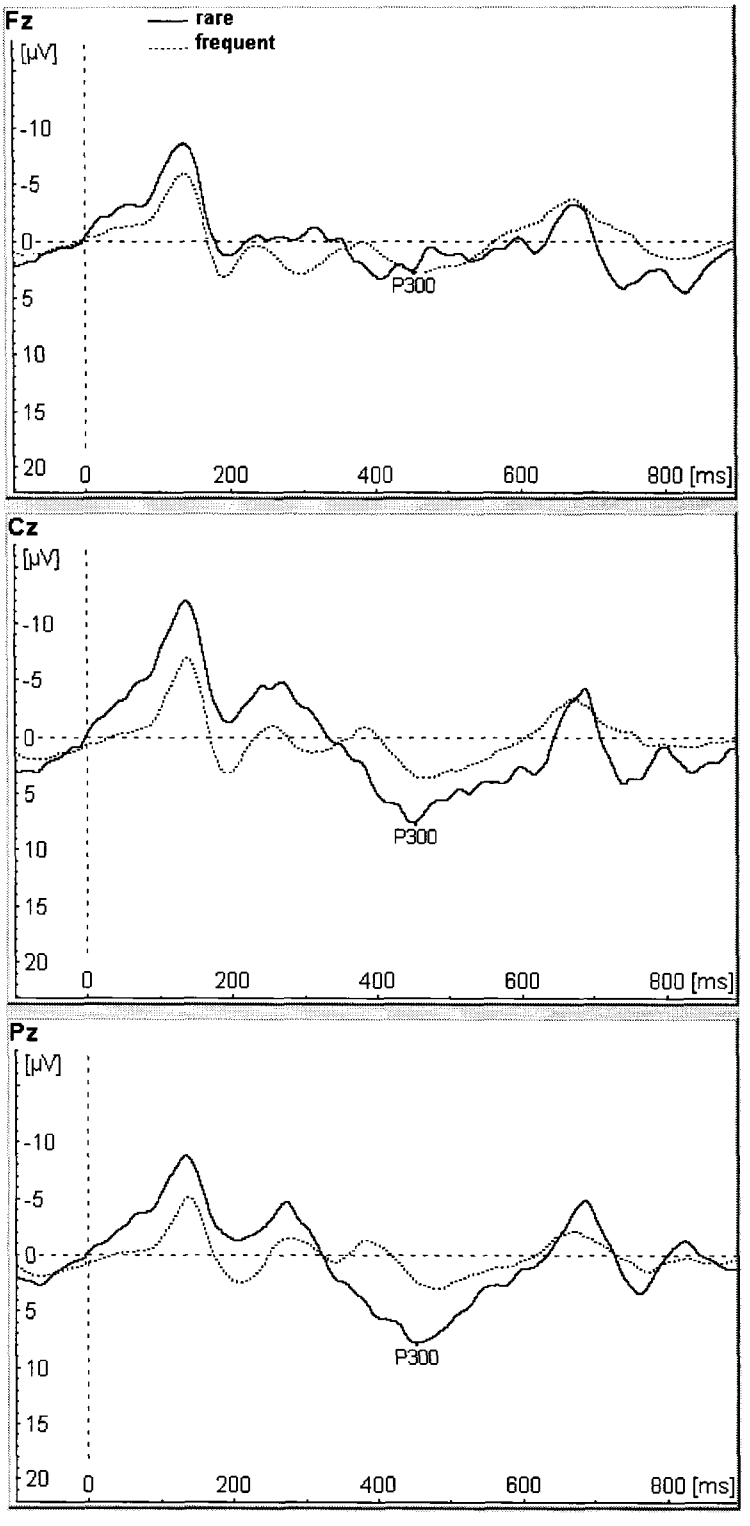

Figure 1. Example of P300 with rare (deviant) and frequent (standard) waveforms in a single subject at midline sites (F_z, C_z, P_z).

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2.7 Statistical Analyses

Power and Precision Software Program [Berenstein, Rothstein & Cohen, 2001] was used for sample size computations. Based on four assumptions (family-wise alpha =.05; one-sided tests; ability to detect medium sized effects; and adjustment for multiple measures), power calculations indicated that a sample of n = 15/group will have power of 90% to yield a significant allele x nicotine interaction for ERP measures. Three separate analyses (using Statistical Package for Social Sciences [SPSS 14.0]) were carried out for each of the endophenotype paradigms, one involving group comparison of baseline measures, and the second involving group comparison of post-baseline measures, and the third grouping regional electrode sites and comparing post-baseline measures. Each analysis involved the use of analyses of variance (ANOVAs) procedures, with gender and allele type acting as between group factors and electrode site and gum type acting as within-group factors. Analysis of co-variance (ANCOVAs) was to be employed if it was not possible to match groups on N, E, P, ES and DIS trait factors, with scores on these factors serving as covariates. Significant ($p < .05$) ANOVA/ANCOVA effects were followed-up with univariate ANOVAs/ ANCOVAs being carried out on each dependent measure, and any significant Greenhouse-Geisser corrected effects were further examined with Bonferroni-adjusted pairwise comparisons.

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3.0 Results

3.1 Demographic and Personality Measures

Independent analysis of age, gender, IQ, the three subscales of the Eysenck Personality Questionnaire (extraversion, psychoticism, neuroticism) and two subscales of the Sensation Seeking Scale V (experience seeking, disinhibition) found no significant differences between groups. Thus these measures were not employed as covariates in subsequent analysis of variance. Table 1 displays the mean (± S.E.) characteristics of the two allele groups.

Table 1. Means (±S.E.) for demographic and personality factors

	A1/A1 and A1/A2	A2/A2
Age	24.8 (±1.4)	24.4 (±1.2)
IQ		
VIQ	110.3 (±2.1)	112.8 (±1.7)
PIQ	110.7 (±1.0)	111.9 (±0.8)
FSIQ	111.7 (±1.8)	113.9 (±1.5)
EPQ scores		
Extraversion	13.3 (±2.0)	14.3 (±1.7)
Psychoticism	6.0 (±0.9)	8.1 (±0.8)
Neuroticism	9.7 (±1.5)	11.1 (±1.3)
SSS-V scores		
ES	5.6 (±0.5)	6.0 (±0.5)
DIS	3.3 (±0.8)	4.5 (±0.6)

3.2 Mood Measures

A gum effect $F(1,22) = 4.3$, $p<0.05$ found that nicotine gum (M =6.1, S.E. =0.3) increased alertness relative to placebo gum (M= 5.5, S.E. =0.3). Although it did not reach significance, a gum by time interaction revealed a trend towards increased alertness post gum administration, with nicotine increasing ($p<0.02$) alertness (M= 6.4, S.E. =0.3)

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compared to placebo gum (M= 5.4, S.E. =0.3), as illustrated in Figure 2. Statistical analysis of the other mood measures, contented and calm, was not significant.

3.3 Behavioural Performance Measures

In general, participants performed the RVIP with reasonable accuracy, exhibiting hits rates of 83.6 % on average. Analysis of rates of correct detections and false alarms did not reveal any significant effects or interactions.

Reaction time, rates of correct detections to target stimuli and false alarms were assessed in the A1 versus the A2 group as a function of gum. Analysis of reaction time revealed no significant effects or interactions, however planned comparisons revealed gum effects were dependent on allele group and time interaction ($p<0.01$) which is depicted in Figure 3. Post nicotine administration (M= 437.5 ms, S.E. =14.8) in the A1 group resulted in slower ($p<0.01$) reaction times compared with baseline reaction times (M= 459.4 ms, S.E. =15.6). In the A2 group, reaction times at post nicotine administration (M= 443.5 ms, S.E. =12.5) was found to be faster ($p<0.001$) relative to baseline (M= 467.8 ms, S.E. =13.2) and reaction times post placebo (M= 435.9 ms, S.E. =14.4) administration was shortened ($p<0.02$) relative to baseline reaction times (M= 453.9 ms, S.E. =14.4).

3.4 ERP Measures

3.4.1 P300 Amplitude

The analysis of ERP amplitudes was carried twice, one analysis using amplitude data from the three conventional midline scalp sites, F_z, C_z and P_z, and one analysis

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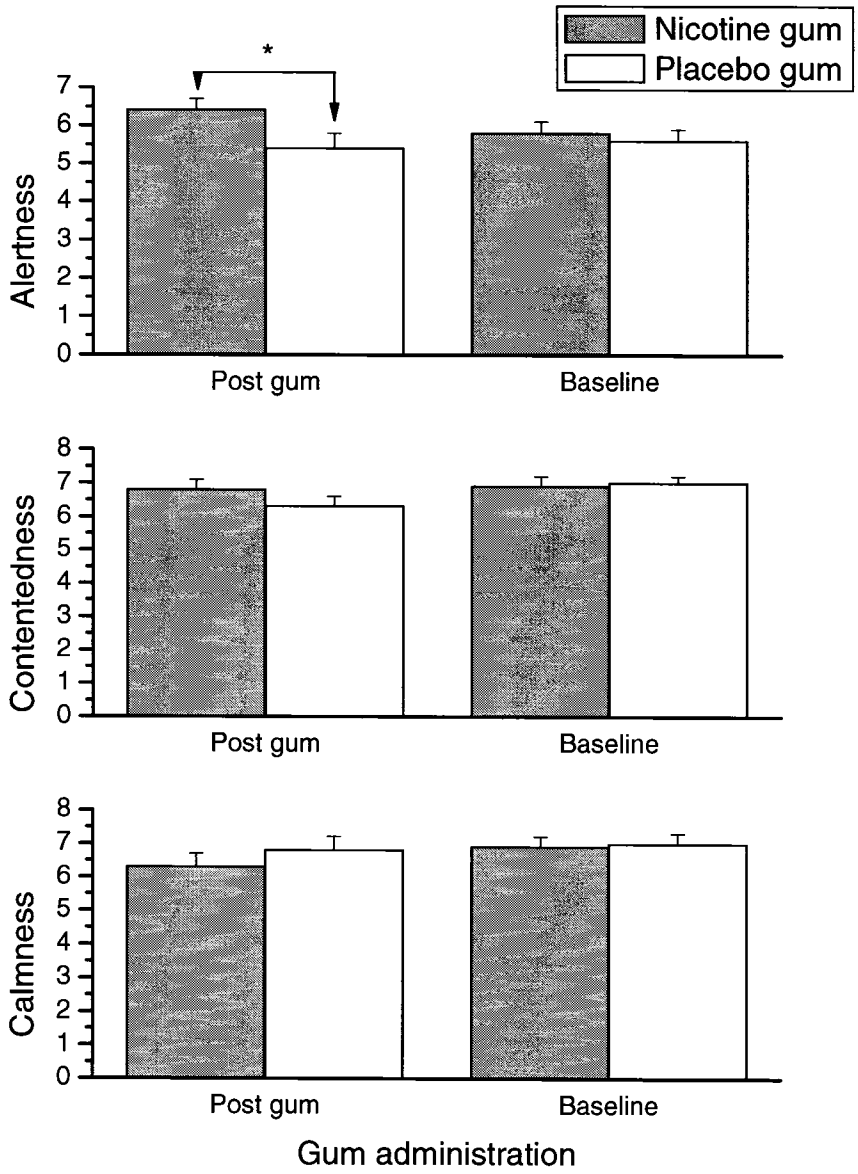

Figure 2. Subjective measures of alertness, contentedness and calmness in nicotine and placebo conditions sessions, at baseline and post-gum administration.

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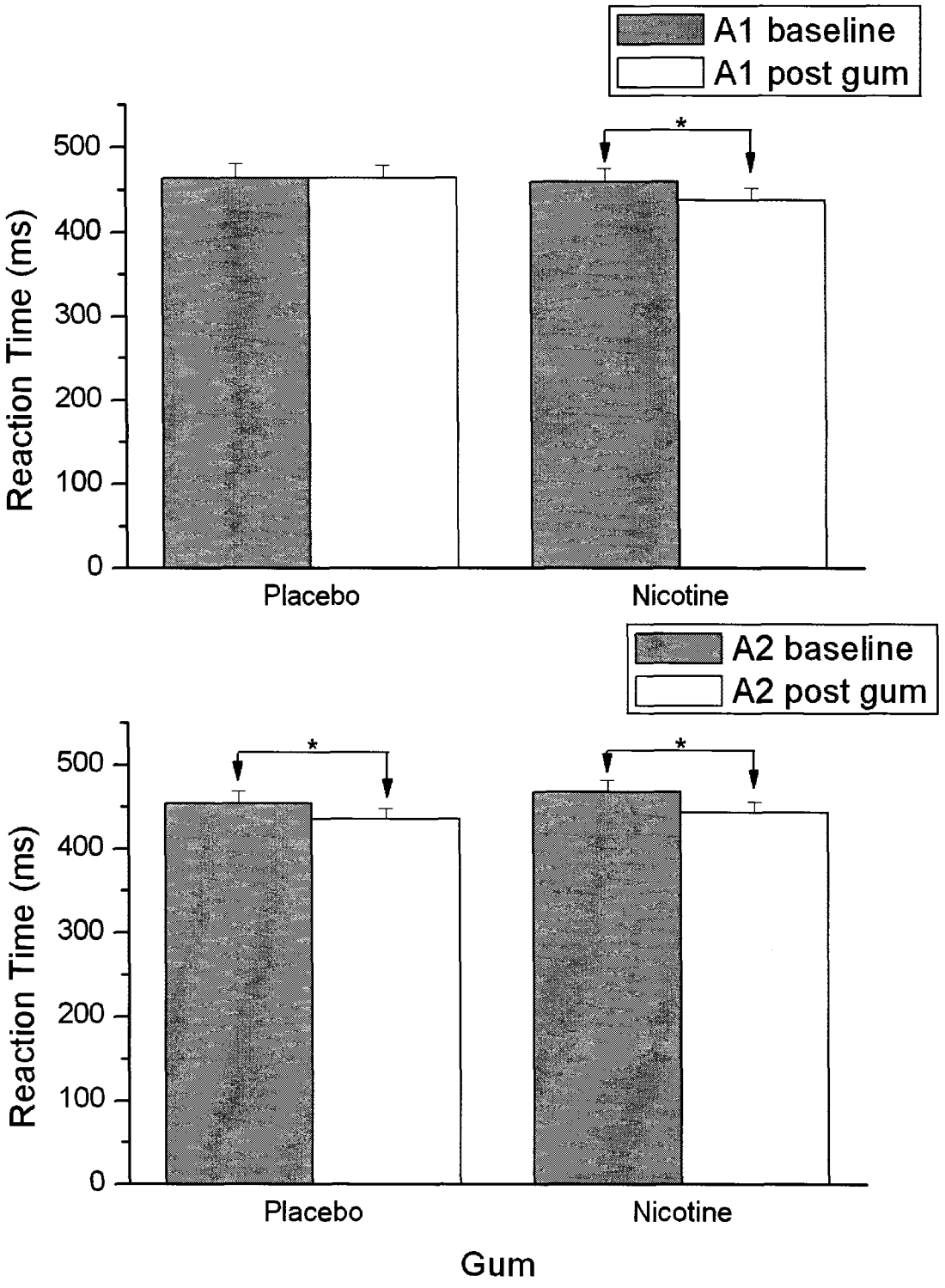

Figure 3. Reaction time (ms) to deviant stimuli in A1 and A2 groups in nicotine and placebo conditions sessions, at baseline and post-gum administration.

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looking at regional effects across the scalp by grouping electrode data from left (F3, F7) and right (F4, F8) frontal and left (P3, P7) and right (P4, P8) parietal sites. Analysis of P300 amplitudes at the three midline sites revealed a site effect $F(1,22) = 66.6$, $p<0.001$, with amplitudes increasing from anterior to posterior. Parietal (Pz) (M =4.7μV, S.E. =0.5) amplitudes were found to be significantly larger than both central (Cz) (M =3.7μV, S.E. =0.5) and frontal (Fz) (M =1.5μV, S.E. =0.3) amplitudes. Central amplitudes were also found to be significantly larger than frontal amplitudes. Planned comparisons at Pz did not reveal any significant effects. The grand averaged waveforms at Pz are presented in Figure 4, displaying the P300 component in both allele groups, at baseline and post gum in placebo and nicotine conditions.

Statistical analysis with site groupings did not reveal any significant findings, nor did subsequent planned comparisons.

3.4.2 P300 Latency

No significant findings were revealed in the ANOVA or in planned comparisons of P300 latency.

3.5 Vital Signs

Analysis of heart rate revealed an effect of time (baseline versus post-gum administration) $F(1,22) = 10.9$, $p<0.01$ which was qualified by a time by allele interaction $F(1,22) = 15.8$, $p<0.01$. After gum administration, heart rate (M =67.9 bpm, S.E. =2.2) was elevated relative to baseline (M =61.8 bpm, S.E. =1.3) in the presence of the A1 allele (A1/A1 or A1/A2). In addition, the A1 group (M =67.9 bpm, S.E. =2.2) had elevated heart rate relative to the A2 group (A2/A2) (M =60.9 bpm, S.E. =1.9) post

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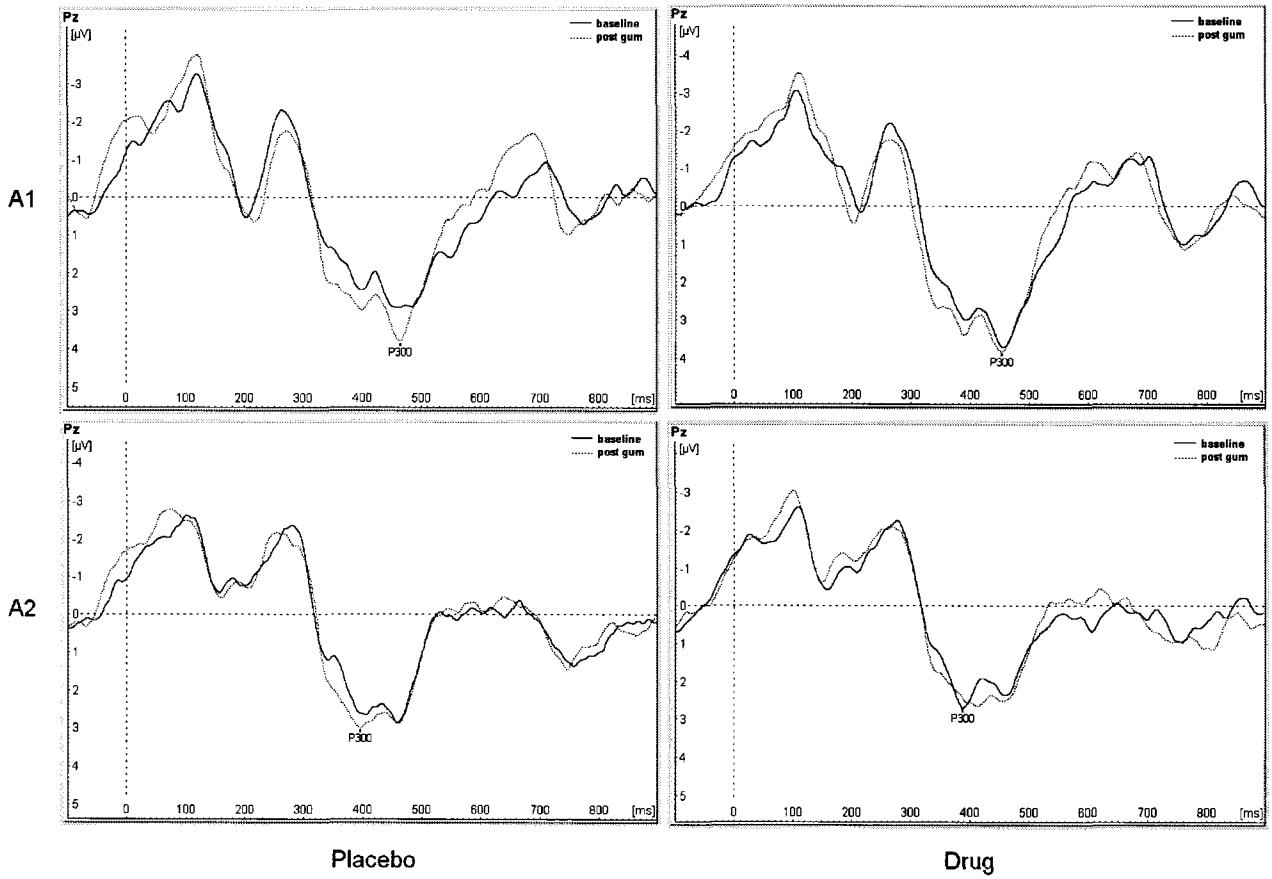

Figure 4. P300 deviant waveforms in A1 and A2 groups at baseline and post gum in nicotine and placebo conditions at P_z.

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gum administration. A time by gum interaction $F(1,22) = 9.8$, $p<0.01$ was found, with nicotine increasing heart rate post gum (M =67.0 bpm, S.E. =2.0) administration relative to baseline (M =61.7 bpm, S.E. =1.5) and post gum administration, nicotine (M= 67.0, S.E. =2.0) was found to increase heart rate relative to placebo gum (M =61.8 bpm, S.E. =1.5).

Neither systolic nor diastolic measures of blood pressure resulted in any significant main effects or interactions.

3.6 Adverse Reactions

Analysis of variance did not result in significant differences, however planned comparisons revealed that in the A2 group, adverse reactions were greater ($p<0.02$) post nicotine (M =1.9, S.E. =0.2) relative to post placebo (M =1.2, S.E. =0.2) administration.

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4.0 Discussion

Nicotine is thought to exert its effects on attention in part via dopaminergic activity and attempts have been made to more precisely characterize dopaminergic involvement in this cognitive domain. In this regard, the current study examined the relationship between the DRD2 Taq1A polymorphism and nicotine-induced attentional alterations by probing RVIP in nonsmokers using behavioural performance and electrophysiological measures to assess attention. Although the results do not fully concur with either the proposed hypotheses or current literature with respect to allele group differences, they were nonetheless informative. Findings will be discussed in the context of underlying neurobiology and attentional function and with reference to study limitations.

Despite decreased sensitivity to nicotine's effects which might be expected with reduced DA receptor numbers, the literature suggests instead that the reduced DA receptor density (including DRD2) and general DA hypofunction attributed to the presence of the A1 allele results in an increased propensity to the use of DA-augmenting substances as a compensatory mechanism to normalize the dopaminergic deficit (Anokhin et al., 2000; Gilbert et al., 2005). In previous work, this contention was supported by findings that nicotine, which is associated with increased release of striatal and cortical DA, was shown to improve performance in smokers with the A1 allele (Anokhin et al., 2000; Gilbert et al., 2005), presumably by reducing the DA hypofunction that is the purported baseline state of A1 carriers.

The functional effects of the Taq1A polymorphism have only recently been investigated in relation to dependence, and as such, the available evidence precludes a

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conclusive elucidation of the precise relationship between the dopaminergic system and attentional efficiency and nicotine. Studies employing the DRD2 agonist bromocriptine, have evidenced improved nicotine withdrawal symptoms (Lawford et al., 1995) and increased activation of the mesolimbic reward circuitry, as assessed by PET (Kirsch et al., 2006), in the presence of the A1 allele relative to the A2/A2 genotype. Similarly, nicotine has been demonstrated to improve behavioural performance (Gilbert et al., 2005), and the nicotine patch has been found to be a more effective smoking cessation strategy (Johnstone et al., 2004) in A1 carriers compared to A2 homozygotes. However, treatment of withdrawal in smokers with buproprion hydrochloride, a putative dopamine and norepinephrine reuptake inhibitor and alpha7 nAChR inhibitor, was found to vary as a function of DRD2 Taq1A genotype, with decreases in craving, irritability and anxiety evident only in the A2 homozygotes (David et al., 2003). Although not in concordance with the majority of findings, it is possible that since the actions of buproprion hydrochloride appear to be diverse and are poorly understood, clarifying the relationship between nicotine, dopaminergic function and genotype is difficult. Thus the majority of the available study findings suggest that nicotine improves deficits in A1 carriers.

Nicotine did not impact performance accuracy as indicated by failure to observe any gum effect, with correct detections or false alarm rates. Improved rates of correct detection have been observed in previous studies with cigarette smoking and nicotine administration but these observations have been limited to overnight tobacco deprived smokers. Consistent with other studies (Levin et al., 1998; Warburton & Mancuso, 1998), nicotine decreased reaction times in the present study, however it did so equally in both A1 and A2 allele groups and only in the A1 group was response speed improvement

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limited to nicotine (versus placebo) gum administration. Previous research differentiated allele groups based on nicotine responsivity, as assessed by behavioural performance measures, with the A1 group showing greater nicotine-induced improvements compared to the A2 group (Gilbert et al., 2005). The current results, revealed by planned comparisons, although not entirely in concordance with the proposed hypotheses or with previous findings, nevertheless suggest an intrinsic difference between allele groups. This difference may indicate that a lack of improvement in response speed over time may be a function of general DA hypofunction (including reduced striatal DA receptor density, and reduced DRD2 receptor density) that is putatively associated with the presence of A1 allele.

Neither P300 latency nor amplitude was found to vary as a function of allele or nicotine administration in the current study. However, dopaminergic involvement in smoking has been evidenced in electrophysiological studies as nicotine's electrophysiologically arousing effects in smokers, as evidenced by EEG activation, were partially attenuated following the administration of a DRD2 antagonist (Walker, Mahoney, Ilivitsky, & Knott, 2001). Consistent with this, nicotine has repeatedly been shown to affect P300 measures, with nicotine typically increasing amplitude in smokers (Polich, & Ochoa, 2004), implying a relationship between attentional processing and nicotine-mediated dopaminergic function. Furthermore, deficits in the P300 have been evidenced in the presence of the A1 allele, with reduced P300 amplitudes being observed in smokers with these allele groupings (Anokhin et al., 1999). It has been hypothesized that P300 amplitude in particular modulates the association between the A1 allele and dependence (Anokhin et al., 1999). The finding in at risk children of alcoholics that the

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presence of the A1 allele is related to reduced P300 amplitude suggests that P300-assessed attentional deficits represent a pre-existing state, rather than being a result of dependence (Hill et al., 1998) and thus is supportive of the notion that individuals with the A1 allele have reduced ability to allocate attention. This impairment may be a function of deficits in any of the constituent stages in context updating (attentional allocation, memory updating). It is possible that nicotine-induced attentional facilitation in A1 carriers may compensate for deficits specific to the neurobiology associated with the A1 allele and be mediated by improved dopaminergic function. Thus nicotine dependence may be a means by which individuals with dopaminergic hypofunction (i.e., A1 carriers) alleviate impaired cognitive/attentional tone. This is consistent with the attentional allocation model of nicotine reinforcement, which posits that nicotine facilitates attention by means of its ability to focus attention (e.g., by reducing distractibility), and/or by increasing processing capacity (Kassel, 1997). Although not supported by the results of the current study, it is possible that study-related limitations may have precluded the elucidation of a relationship between DRD2 genotype and nicotine-altered attentional responsivity as assessed by P300 ERPs.

Although nicotine has been found in some task paradigms to improve attention in tasks with high (relative to low) attentional demands regardless of smoker versus non-smoker population (Newhouse, Potter, & Singh, 2004; Warburton & Rusted, 1993), this was not replicated in the present study. However, the general lack of significant findings in the current study does not necessarily contradict previous research. Whereas LeHouezec et al. (1994) found that nicotine improved attentional performance in non-smokers, Newhouse, Potter, & Singh (2004) argue that the preponderance of evidence

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supports differential effects of nicotine in smokers versus non-smokers as the majority of studies reporting performance augmentation due to nicotine employed a sample of tobacco-deprived smokers, while those using a non-smoker sample, typically reported no effects or even impaired performance. An explanation of this finding suggests that nicotine optimizes performance in smokers who perform sub-optimally as a result of withdrawal however, in non-smokers who are already performing optimally, nicotine exerts no enhancing effects and can even disrupt performance (Newhouse, Potter, & Singh, 2004). They argue that this suggests a sub-optimal baseline state in smokers, which may be in part related to altered neurobiology and sensitivity to nicotine (relative to non-smokers) resulting from chronic nicotine exposure or withdrawal-related processes. As nicotine exerts some of its effects via the dopaminergic circuitry, it is feasible that the neurobiological differences between smokers and non-smokers are related to alterations within DA receptor systems which themselves may represent the basis upon which previous study findings, reporting altered cognitive function/performance as a function of TaqIA polymorphism, depend. Studies directly comparing the effects of nicotine in smokers and non-smokers are few in number and have been inconclusive with respect to nicotine's specificity (Foulds et al., 1996; Poltavski & Petros, 2005) but support for nicotine's optimizing properties, independent of tobacco withdrawal, has been forthcoming from Poltavski and Petros (2006) who reported nicotine-related performance improvements in non-smokers with attentional deficits and performance decrements in non-smokers without attentional deficits.

Of note in this study is the fact that subjective alertness was increased following nicotine administration, which is consistent with previously demonstrated arousing

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effects of nicotine (Walker, et al., 2001). These increases indicated that the selected dose, despite being low, was bioavailable and capable of inducing measurable effects, thus suggesting that the lack of expected ERP and behavioural performance effects may not be related to inadequate dosing. It is of interest that subjective alertness increments with nicotine were not allele dependent. Although not measuring alertness per se, previous studies in smoking found subjective ratings of negative affect, including withdrawal, were more responsive to pharmacologic treatment in smokers absent the A1 allele (Cinciripini et al., 2004; David et al., 2003).

Taken together, the findings of the current study do not suggest a role for the A1 allele in nicotine-altered sustained attentional processing in non-smokers. However, these results should be interpreted in the context of the limitations of the study. It is possible that the nature of the sample, including demographic characteristics had an impact on the outcome. Small sample size was a key limiting factor, particularly in the A1 group, as only ten participants were contained within this group, decreasing the statistical power of the study, thus important insights may be gained by repeating the experiment with a larger, more informative sample. A sample of sufficient size to allow for groupings based on additional mediating variables would enable a more thorough description of DRD2 genotype-dependent effects. For example, as gender (Benowitz, & Hatsukami, 1998), personality (Gilbert, & Gilbert, 1995) and smoking status (Newhouse, Potter, & Singh, 2004) have independently been shown to effect nicotine responsivity, future samples should attempt to investigate the potential contribution of these factors. Another variable of interest, the functional differences between the A1/A1, A1/A2 and A2/A2 genotypes, has been identified in a number of studies via altered brain activation

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patterns (Kirsch et al., 2006) and differential DRD2 binding site densities (Noble et al., 1991). These findings, which distinguish between the three genotypes, advocate that future studies should employ allele groupings that distinguish between all three genotypes. It is also important that probable polygenic nature of nicotine dependence provide direction for future studies, supporting the examination of multiple and interacting genetic influences. A second limiting factor relates to nicotine dosing. Only one dose was applied and as a number of studies have found performance changes to be dose-dependent, thus multiple doses should be employed in future studies. Nicotine gum is also a relatively inadequate route of administration as a preparation of nicotine can be swallowed (versus via bucal mucosa), leading to viable levels of absorption (Hukkanen, Jacob, & Benowitz, 2005). Nicotine patch leads to more consistent levels of nicotine but nicotine inhalation results in more rapid absorption and mimics more closely the effects of smoke-inhaled nicotine (Hukkanen, Jacob, & Benowitz, 2005).

Although the findings do not completely preclude differential genotype-dependent attentional effects of nicotine, it is suggested that the differences may be evident only in those subpopulations characterized by attentional deficits. Specifically, it is suggested that nicotine may exert its attention-augmenting effects only in individuals with sub-optimal performance/attentional function and that in the case of attentionally-deficient smokers with the A1 allele, nicotine may facilitate attention possibly by minimizing the DA hypofunction associated with the A1 allele. This discussion highlights the complexity of disorders such as nicotine dependence, which appear to be predicated on multiple interrelated contributing factors and as such is key to informing the direction of

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future research. Approaches employing standardized methodologies that systematically attempt to account or control for these multiple factors are likely the most informative.

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APPENDICES

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6.1 APPENDIX A: INFORMED CONSENT

University of Ottawa
Institute of Mental Health Research
Institut de recherche en santé mentale
de l'Université d'Ottawa

INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title of Study: Dopamine Receptor (DRD2) Genotype-Dependent Effects of Nicotine on Event-Related Potential Indices of Attention During Rapid Visual Information Processing.

Principal Investigator: Anne Millar, B.Sc., M.Sc. candidate

Associate Investigators: Verner J. Knott, Ph.D., C. Psych.
Hymie Anisman, Ph.D.

INTRODUCTION

Please take the time to read carefully and consider the following information before you give your consent to be a research volunteer in this study. This information describes the purpose and procedures, as well as the possible risks and benefits of the research. You are encouraged to discuss any questions with the study investigators and other members of the team. You will receive a copy of this information sheet and the signed consent form if you agree to participate.

BACKGROUND

Anne Millar is conducting a study into the effects of nicotine on thought processes in healthy volunteers. Specifically, the study will attempt to investigate whether a particular variant of a gene (units of DNA that make up the genetic material in cells), the dopamine D2 receptor gene, can influence the effects of nicotine. Dopamine is a chemical which is involved in many biological activities, affecting movement, reward, appetite, thought processes and mood. This research is considered important as it may provide information which will allow the development of more effective treatments for smokers. In this study, 15 non-smokers with the A1 variant of the dopamine D2 receptor gene will be given nicotine gum and will be compared to 15 non-smokers with the A2 variant of the gene. Another goal of this research is to identify the function of other candidate genes that may contribute to a potential difference in response to nicotine, including genes regulating dopamine function (DAT, DRD1, DRD2, DRD4, COMT), serotonin function (5-HTT, 5-HT receptors) and nicotine metabolism (CYP2A6).

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PROCEDURES

Each potential volunteer will undergo a preliminary interview just prior to the first test session, which will begin at 8:00 a.m.. This interview will include a saliva sample, and a questionnaire to obtain information on your own mental and physical health status and on your family psychiatric and health history. All volunteers meeting these study criteria may continue to take part in the study. The second session will be the same as the first with the exception of the interview. As of midnight before each test day, all volunteers will be asked to abstain from food, alcohol, drugs, caffeine.

On one test day, each participant will be given nicotine gum, while on the other test day, the gum will be a placebo (i.e., will be a commercial gum containing no nicotine). The gum will be administered in a random order and under double-blind conditions so that neither the volunteers nor the investigators will be aware of the contents. Assessments will be carried out both before and after the gum is administered. These will involve the completion of A mood questionnaire, and the monitoring of brain electrical activity (EEG) during periods of rest and during the presentation of visual stimuli, some of which volunteers will be required to respond to by pressing a computer mouse key. The EEG measures will provide some insight into the effects of nicotine on brain function and thought processes like attention, which can be affected by genetics.

The duration of each test session will be approximately 2½ hours, ending by ~10:30 a.m., and volunteers are encouraged to call the lab if they experience any adverse symptoms.

At an external laboratory (Dr. Paul Albert's laboratory at the Ottawa Health Research Institute), DNA extracted from the saliva sample will be analyzed to determine the variant of the DRD2 gene (i.e., the A1 or the A2 variant).

POTENTIAL RISKS

Nicotine gum is typically used by smokers attempting to quit smoking. Two pieces of gum will be given, a 4 mg and a 2 mg piece, for a total of 6 mg of nicotine. You will be asked to chew the gum, following pre-recorded chewing instructions, for 30 minutes. This is a standard recommended dose for smokers using gum to stop smoking. Nicotine from gum is absorbed slowly, and, as such, it has a very low potential for abuse. Nicotine gum can induce temporary throat irritation and may also cause temporary nausea, abdominal pain, dizziness, headache, tremors, heart palpitations and cold sweating.

The EEG (brain wave) monitoring is very similar to what is carried out in general hospitals except that it is analyzed with a computer. The electrodes placed on your scalp and around the eyes to monitor EEG activity may cause a mild and temporary irritation and redness of the skin which disappears after a few hours.

During the interview session, approximately 2 milliliters of saliva will be collected for genetic analysis to assess whether individual differences in genes controlling the

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functioning of brain dopamine, serotonin (receptors and transporters) affect the response to nicotine.

POTENTIAL BENEFITS

There are no immediate mental health benefits for participating in this study. It is hoped that the results from this study will provide some insight into the relationship between smoking and genetics and will also help to evaluate the role of nicotine-like drugs as a possible treatment strategy for smoking cessation. Upon completion of all aspects of the study, all volunteers will receive $50.00 to cover their time and effort in the study.

PARTICIPATION

If you do decide to take part in this study, you participation is voluntary and you may withdraw from the study at any time.

CONFIDENTIALITY

All information and data collected, including the saliva samples, will be coded to protect your privacy. This information will be stored in the Neuroelectrophysiology and Neuropharmacology Laboratories for up to 15 years. This will be available only to the personnel in this study.

The genetic information will be coded with an identification number, and stored Neuropharmacology Laboratories until genetic analysis is completed at Dr. Paul Albert's laboratory. These samples will be used only for the stated purposes of the study and will be available only to the personnel in this study.

No identifying information will be released without your permission. Any scientific publication or presentation resulting from this work will be presented in such a manner so as not to disclose your identity.

INFORMATION

If you have any specific questions about his research, you should contact Anne Millar or Dr. Knott, who can be reached by telephone at (613) 722-6521 ext 6254.

This study has been reviewed by the Research Ethics Board (REB) of the Royal Ottawa Mental Health Centre. If you have any general questions regarding the ethics of this study, you may contact the Chairman of the REB, Dr. Alan Douglass at (613) 722-6521. ext 6226.

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CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

Title of Study: **Dopamine Receptor (DRD2) Genotype-Dependent Effects of Nicotine on Event-Related Potential Indices of Attention During Rapid Visual Information Processing.**

Principal Investigator: **Anne Millar, B.Sc., M.Sc. candidate**

Associate Investigators: **Verner J. Knott, Ph.D., C. Psych.**
Hymie Anisman, Ph.D.

I, _____, agree to participate in the above described research project, the nature and possible complications of which have been explained to me as outlined in the attached informed consent.

I agree to abstain from caffeine, drugs and food beginning at midnight prior to each of the two morning test sessions.

I understand that the possible effects of nicotine administered in the study are temporary.

I understand that any data collected as a result of my participation in this study may be used for scientific presentations or publications. I have received assurance that my anonymity will be preserved in the use of this material.

I have also received assurance that I may keep a copy of this consent form (with one copy being kept by the study investigators) and that I may withdraw from participation at any time.

Name of Volunteer (printed)	Signature of Volunteer	Date
Name of Investigator (printed)	Signature of Investigator	Date
Name of Witness (printed)	Signature of Witness	Date

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6.2 APPENDIX B: SCREENING QUESTIONNAIRE

DRD2 Study

Telephone screen questionnaire

Date:_____ ID#_____

Name_____

Age_____ D.O.B (mm/dd/yy)_____ Sex_____

Handedness_____ Normal hearing:_____ Normal/corrected vision

Telephone: h:_____

w:_____

Address:_____

EXCLUSION CRITERIA

_____Are you currently on medication on a regular basis for any physical condition?
_____Have you ever sought treatment for emotional problems?
If yes:
_____Are you still being seen for treatment?
_____Do you currently receive medication for these problems?
_____Have you had a brain disorder, like epilepsy?
_____Have you had a head or brain injury in the past two years?
If yes, did you lose consciousness for one or more hours?
_____Do you have diabetes?
_____Do you have any serious allergies?
_____Have you had surgery in the past six months?
_____Have you been diagnosed with cardiac or respiratory conditions?
_____What is your daily alcohol consumption?
_____Do you use street drugs?
If yes, how often?_____ and what drugs?
_____
_____Are you pregnant? Nursing?
_____Have you ever been treated for drug or alcohol abuse?

Non-smokers:

_____How many cigarettes have you smoked in your lifetime(<10 cigs, or other tobacco)?
_____Have you smoked any cigarettes in the last year (none)?

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6.3 APPENDIX C: BOND AND LADER

Bond & Lader

Date:_____ ID#:_____

Test session:_____ Assessment #:_____

Please rate the way you felt during the task in terms of the dimensions given below. Regard the line as representing the full range of each dimension. Mark clearly and perpendicularly across each line.

Alert _____ Drowsy

Calm _____ Excited

Strong _____ Feeble

Muzzy_____ Clear-headed

Well-coordinated_____ Clumsy

Lethargic_____ Energetic

Contented _____ Discontented

Troubled_____ Tranquil

Mentally Slow _____ Quick-witted

Tense _____ Relaxed

Attentive _____ Dreamy

Incompetent _____ Proficient

Happy _____ Sad

Antagonistic _____ Amicable

Interested _____ Bored

Withdrawn _____ Gregarious

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6.4 APPENDIX D: ADVERSE SYMPTOMS

Date: _____ ID:_____ Session:_____

Please rate how you have felt **since chewing the gum** by circling **one** of the following five options, as they relate to the severity of possible nicotine-related symptoms you may or may not have experienced.

1 – No symptoms at all

2 – Mild symptoms (i.e. slight jitters)

3 – Moderate symptoms (i.e. jittery, slight dull headache)

4 – Moderately severe symptoms (i.e. jittery, dull headache, mild nausea)

5 – Severe symptoms (i.e. jittery, dull or pounding headache, nausea, vomiting)

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6.5 APPENDIX E: SSS-V

SSS-V
Date:_____ ID#:_____ Test session:_____

Please read the following pairs of statements and fill in the circle beside the answer that best describes how you feel. Please respond to all statement pairs.

1. O I like 'wild' uninhibited parties
   O I prefer quiet parties with good conversation.

2. O There are some movies I enjoy seeing a second or even third time.
   O I can't stand watching a movie that I've seen before.

3. O I often wish I could be a mountain climber.
   O I can't understand people who risk their necks climbing mountains.

4. O I dislike all body odours.
   O I like some of the earthy body smells.

5. O I get bored seeing the same old faces.
   O I like the comfortable familiarity of everyday friends

6. O I like to explore a strange city or section of town by myself, even if it means getting lost.
   O I prefer a guide when I am in a place I don't know well.

7. O I dislike people who do or say things just to shock or upset others.
   O When you can predict almost everything a person will do or say he or she must be a bore.

8. O I usually don't enjoy a movie or play where I can predict what will happen in advance.
   O I don't mind watching a movie or play where I can predict what will happen in advance.

9. O I have tried marijuana or would like to.
   O I would never smoke marijuana.

10. O I would not like to try any drug which might produce strange and dangerous effects on me.
    O I would like to try some of the new drugs that produce hallucinations.

11. O A sensible person avoids activities that are dangerous.
    O I sometimes like to do things that are a little frightening.

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12. O I dislike 'swingers' (people who are uninhibited and free about sex).
    O I enjoy the company of real 'swingers'.

13. O I find that stimulants make me uncomfortable.
    O I often like to get high (drinking liquor or smoking marijuana).

14. O I like to try new foods that I have never tasted before.
    O I order the dishes with which I am familiar, so as to avoid disappointment and unpleasantness.

15. O I enjoy looking at home movies or travel slides.
    O Looking at someone's home movies or travel slides bores me tremendously.

16. O I would like to take up the sport of water skiing.
    O I would not like to take up the sport of water skiing.

17. O I would like to try surf board riding.
    O I would not like to try surf board riding.

18. O I would like to take off on a trip with no preplanned or definite routes, or timetable.
    O When I go on a trip, I like to plan my route and timetable fairly carefully.

19. O I prefer the 'down to earth' kinds of people as friends.
    O I would like to make friends in some of the 'far out' groups like artists or 'punks'.

20. O I would not like to learn to fly an aeroplane.
    O I would like to learn to fly an aeroplane.

21. O I prefer the surface of the water to the depths.
    O I would like to go scuba diving.

22. O I would like to meet some persons who are homosexual (men or women).
    O I stay away from anyone I suspect of being 'gay or lesbian'.

23. O I would like to try parachute jumping.
    O I would never want to try jumping out of a plane with or without a parachute.

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24. O I prefer friends who are excitingly unpredictable.
    O I prefer friends who are reliable and predictable.

25. O I am not interested in experience for its own sake.
    O I like to have new and exciting experiences and sensations even if they are a little frightening, unconventional or illegal.

26. O The essence of good art is in its clarity, symmetry of form and harmony of colours.
    O I often find beauty in the 'clashing' of colours and irregular forms of modern paintings.

27. O I enjoy spending time in the familiar surroundings of home.
    O I get restless if I have to stay around home for any length of time.

28. O I like to dive off the high board.
    O I don't like the feeling I get standing on the high board (or I don't go near it at all).

29. O I like to date members of the opposite sex who are physically exciting.
    O I like to date members of the opposite sex who share my values.

30. O Heavy drinking usually ruins a party because some people get loud and boisterous.
    O Keeping the drinks full is the key to a good party.

31. O The worst social sin is to be rude.
    O The worst social sin is to be a bore.

32. O A person should have considerable sexual experience before marriage.
    O It's better if two married persons begin their sexual experience with each other.

33. O Even if I had the money, I would not care to associate with flighty rich persons like those in the 'jet set'.
    O I could conceive of myself seeking pleasures around the world with the 'jet set'.

34. O I like people who are sharp and witty even if they do sometimes insult others.
    O I dislike people who have their fun at the expense of hurting the feelings of others.

35. O There is altogether too much portrayal of sex in movies.
    O I enjoy watching many of the 'sexy' scenes in movies.

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36. ○ I feel best after taking a couple of drinks.
    ○ Something is wrong with people who need liquor to feel good.

37. ○ People should dress according to some standard of taste, neatness and style.
    ○ People should dress in individual ways even if the effects are sometimes strange.

38. ○ Sailing long distances in small sailing crafts is foolhardy.
    ○ I would like to sail a long distance in a small but seaworthy sailing craft.

39. ○ I have no patience with dull or boring persons.
    ○ I find something interesting in almost every person I talk to.

40. ○ Skiing down a high mountain slope is a good way to end up on crutches.
    ○ I think I would enjoy the sensations of skiing very fast down a high mountain slope.

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