Neuroelectrical investigations into the sensory and cognitive effects of nicotine and monoamine oxidase inhibition in humans

Dylan Smith

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Department of Neuroscience

Faculty of Cellular & Molecular Medicine

University of Ottawa

ABSTRACT

Investigations into the cognitive effects of tobacco smoking have generally focused on nicotine and its effect on nicotinic acetylcholine receptors (nAChRs) in the brain. However, it is now known that chronic smokers exhibit robust inhibition of the monoamine oxidase (MAO) enzyme through the actions of non-nicotine components in tobacco smoke. Therefore, the primary aim of this thesis is to elucidate the effects of nicotine and MAO-inhibition on electroencephalographic (EEG) and event-related potential (ERP) measures of cognition. 24 healthy nonsmoking males were administered 75 mg of moclobemide, and chewed 6 mg nicotine gum, in order to simulate the effects of acute smoking. Four experimental conditions included placebo, nicotine, moclobemide, and a combination of nicotine and moclobemide. Early auditory ERPs were used as measures of cognition, such as the auditory P50 sensory gating paired-stimulus paradigm, the acoustic-change-elicited mismatch-negativity (MMN), the novel sound-elicited P3a, and the target sound-elicited P3b. Three minutes of eyes closed EEG were also recorded. Because these ERPs are often identified as biomarkers for schizophrenia, drug effects were also measured after individuals were stratified for low-baseline amplitude of each ERP measure, as a laboratory model of cognitive deficits in schizophrenia. Overall results showed a synergistic improvement in sensory gating via nicotine combined with moclobemide, accompanied by a reduction in theta band power. Nicotine in the absence of moclobemide increased P3b amplitude, accompanied by an increase in $alpha_2$ band power. Moclobemide in the absence of nicotine increased P3a amplitude, accompanied by a decrease in $beta_2$ power. Stratifying participants by placebo

amplitude revealed both nicotine and moclobemide exhibited an inverted-U pattern of effect, i.e. showing greater amplitude increases in individuals with the lowest baseline amplitudes. Overall, this thesis demonstrates how these two components of tobacco smoke affect different facets of auditory processing in different ways, with synergistic effects in some paradigms but antagonizing effects in others. Therefore, chronic smokers and schizophrenia patients who seek transient cognitive improvement through smoking may actually experience cognitive detriments overall, possibly contributing to withdrawal symptoms and/or an exacerbation of already-present psychiatric symptoms.

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I. **Smith, D. M.,** Fisher, D., Blier, P., Illivitsky, V., & Knott, V. (2014). The separate and combined effects of monoamine oxidase inhibition and nicotine on P50 sensory gating. *Psychopharmacology*, 232, 1911-1920.

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LIST OF ABBREVIATIONS

µV	**micro volt**
5-HT	**serotonin**
ACh	**acetylcholine**
AD	**Alzheimer's disease**
ANOVA	**analysis of variance**
ATD	**acute tryptophan depletion**
BMI	**body mass index**
CDP-choline	**5'-diphosphocholine**
CNS	**central nervous system**
CO	**carbon monoxide**
COMT	**catechol O-methyltransferase**
DA	**dopamine**
DAT	**dopamine transporter**
dB	**decibel**
dHG	**high gating by P50 difference**
DHPG	**3,5-dihydroxyphenylglycine**
dLG	**low gating by P50 difference**
DMT	**dimethyltryptamine**
dP50	**P50 amplitude difference**
EEG	**electroencephalogram**
ERP	**event-related potential**
FIGS	**family interview for genetic studies**

GABA	**gamma-amino butyric acid**
HEOG	**horizontal electro-oculographic**
HG	**high gating**
LG	**low gating**
LTD	**long term depression**
LTP	**long term potentiation**
mAChR	**muscarinic acetylcholine receptor**
MAO	**monoamine oxidase**
MATRICS	**measurement and treatment research to improve cognition in schizophrenia**
Met	**methionine**
MMN	**mismatch negativity**
MNic	**moclobemide/nicotine**
MP	**moclobemide/placebo**
mPFC	**medial prefrontal cortex**
NA	**norepinephrine**
nAChR	**nicotinic acetylcholine receptor**
NET	**norepinephrine transporter**
NMDA	**N-methyl-d-aspartate**
NMDAR	**N-methyl-D-aspartate receptor**
NSERC	**natural sciences and engineering research council of canada**
PET	**positron emission tomography**
PFC	**prefrontal cortex**

phencyclidine	**PCP**
PNic	**placebo/nicotine**
PP	**placebo/placebo**
rHG	**high gating by P50 ratio**
rLG	**low gating by P50 ratio**
rP50	**P50 amplitude ratio**
SCID-NP	**structured clinical interview for DSM-IV-R non-patient edition**
SE	**standard error**
SePhaChARNS	**selective pharmacological chaperoning of acetylcholine receptor and stoichiometry**
SERT	**serotonin transporter**
SPL	**sound pressure level**
SPSS	**statistical package for social sciences**
SSRI	**selective serotonin reuptake inhibitor**
SZ	**schizophrenia**
UMRF	**University of Ottawa medical research fund**
Val	**valine**
VEOG	**vertical electro-oculographic**
VMAT	**vesicular monoamine transporters**
VTA	**ventral tegmental area**

THESIS FORMAT

In accordance with the guidelines set forth by the Faculty of Graduate and Postdoctoral Studies, this dissertation is presented as a collection of manuscripts. This thesis includes four research papers examining the effects of four drug conditions in the same set of healthy volunteers. The first three papers examine different aspects of auditory processing and cognition in each of these drug conditions, and the last paper investigates the effect of these drug conditions on resting state brain activity in the absence of external stimuli. A general introduction precedes the research papers and provides a review of relevant literature pertaining to smoking, cognition, and monoamine oxidase. This section also outlines the major objectives of the thesis. The four research papers follow the general introduction, reproduced as they appear in the published article or submitted manuscript, and each includes their own introduction, methodology, results, and discussion sections. The thesis concludes with a general discussion, including a summary of all results, as well as an overall discussion of all findings in the context of the aims of the thesis as a whole. Implications, limitations, and possible future directions are also discussed in this section.

CHAPTER 1

General Introduction

1.1. Overview

Tobacco use remains the leading cause of preventable death worldwide (World Health Organization, 2011), and yet, approximately one in five people smoke (Centers for Disease Control and Prevention, 2009). While the majority of smokers have reported a desire to quit, over 75% relapse within 6 months of cessation (Zhou et al, 2009). Smoking cessation has been associated with decreases in depression, stress, as well as improvements in affect and psychological quality of life (Taylor et al, 2014), and paradoxically, individuals who continue to smoke often report doing so in order to improve affect, decrease depression, and reduce stress (Berlin et al, 2003). Recently, withdrawal-induced cognitive deficits have been a central focus of smoking dependence (Ashare et al, 2014), and these deficits have been proposed as a potential target for smoking cessation pharmacotherapies (Lerman et al, 2007; Sofuoglu, 2010). Schizophrenia (SZ), a neurological disorder associated with both cognitive deficits (Keefe and Harvey, 2012) and a high prevalence of tobacco use (Dalack et al, 1998), has been the subject of numerous recent studies focusing on nicotinic stimulation (Freedman, 2014). The event-relate-potential (ERP) technique has been a particularly useful method for examining the effects of nicotine, both in SZ patients and non-clinical populations, due to its high temporal sensitivity (Luck, 2012). As such, nicotinic effects have been observed in many auditory ERP paradigms, including sensory gating as measured by the auditory P50 (Knott et al, 2013), sensory memory as measured by the mismatch negativity (MMN) (Knott et al, 2014a), and attention as measured by the P300 (Knott et al, 2014b). Effects on baseline state resting EEG have also been shown (Fisher et al,

2012). However, while the neuropsychopharmacological effects of smoking are most commonly associated with nicotine, it is now known that tobacco use is also associated with robust monoamine oxidase (MAO) inhibition (Berlin and Anthenelli, 2001), a state which itself may alter cognitive processing (Wesnes et al, 1988). Currently, the degree to which MAO inhibition contributes to the cognitive effects of smoking is not known.

1.2. Nicotine and the brain

1.2.1. Nicotine delivery via smoking

Nicotine is the main alkaloid found in the tobacco plant. It comprises approximately 95% of the total alkaloid content in commercial cigarettes; making up ~1.5% of total tobacco weight. (Benowitz, Hukkanen, and Jacob, 2009). Cigarettes of average nicotine content contain approximately 10-14 mg of nicotine (Kozlowski et al, 1998), and of this, 1-1.5 mg is absorbed during smoking (Benowitz and Jacob, 1984). A single puff from a cigarette results in rapid absorption of nicotine through the lungs, allowing the drug to cross the blood-brain barrier within 10-20 seconds (Benowitz, 1990). This rapid delivery mechanism allows the user to titrate the precise amount of nicotine desired for a maximal stimulating effect, and for this reason, smoking has the highest potential for addiction compared to other methods of nicotine delivery (Henningfield and Keenan, 1993). Once in the brain, nicotine exerts its actions through activation and desensitization of nicotinic acetylcholine receptors (nAChRs).

1.2.2 Nicotinic Acetylcholine Receptors

1.2.2.1 Structure and function

Brain nAChRs are ionotropic, excitatory, cation-selective pentameric receptors, with acetylcholine (ACh) acting as an endogenous ligand, and which exist as either heteromeric combinations of subunits (α2 - α10; β2 - β4), or as the homomeric α7 type receptor (Toyohara et al, 2013). Each receptor contains two ligand binding sites, located between α and β subunits in heteromers and between α subunits in homoners (Celie et al, 2005). The presence, order, and stoichiometry of each type of subunit within the nAChR alters the biophysical and pharmacological response profile of the receptor (Miwa, Freedman, and Lester, 2011). In the human brain, the two most abundant nAChRs are the heteromeric α4β2 and the homomeric α7 subtypes (Millar and Gott, 2009). In general, the α4β2 subtype has a high affinity to ACh and nicotine, desensitizes at blood/nicotine concentrations in the range experienced by smokers, and exhibits low calcium permeability. The α7 subtype has a low affinity to ACh and nicotine, does not desensitize at moderate smoking concentrations, and is highly permeable to calcium when activated (Poorthuis et al, 2009; Fucile, 2004).

Most, but not all, nAChRs are located presynaptically, and are involved in the release of dopamine (DA), serotonin (5-HT), glutamate, gamma-amino butyric acid (GABA), and norepinephrine (NA) (Dani and Bertrand, 2007). Presynaptic nAChRs enhance neurotransmitter release through mediation of calcium influx into the cell, thereby

triggering calcium-induced calcium release from presynaptic calcium stores (Vernino, 1994; Sharma and Vijayaraghavan, 2003). Because nAChRs are ligand-gated but not voltage-gated, their function is sometimes described as complementary to N-methyl-d-aspartate (NMDA) receptors, as these receptors also modulate calcium influx but only at depolarized membrane potentials (Broide and Leslie, 1999; Dingledine et al, 1999). The coincidence of nAChR stimulation and electrically-induced NMDA receptor activation can lead to an increase of neurotransmitter release at glutamatergic terminals resulting in the induction of long-term potentiation (LTP) (Fisher and Dani, 2000; Dani and Bertrand, 2007).

NAChRs have also been shown to function elsewhere on the neuron, including preterminal and axonal membrane, dendrites, and soma (Albuquerque et al, 2000; Zarei et al, 1999). Preterminal nAChR activation can initiate action potentials by local depolarization and subsequent calcium influx, promoting neurotransmitter release particularly at GABAegic synapses (Lena, Changeux, and Mulle, 1993). NAChRs located on axons and dendrites, can modulate action potential efficiency and spread of neuronal excitation through local alterations of membrane impedance, thus "guiding" neuronal excitation by, for example, inactivating voltage dependant channels at neuronal or dendritic bifurcations (Dani and Bertrand, 2007).

1.2.2.2 Distribution of cholinergic signalling

Three major cholinergic pathways exist in the central nervous system (CNS) which project ACh to nearly every area of the brain (Woolf, 1991). Pedunculopontine tegmental

neurons and laterodorsal pontine tegmental neurons innervate the thalamus and midbrain dopaminergic areas such as the ventral tegmental area (VTA) (Oakman et al, 1995). A second pathway originates at cholinergic densities in the basal forebrain and broadly innervates the cortex and hippocampus (Selden et al, 1998). The third pathway involves striatal cholinergic neurons which innervate the striatum and olfactory tubercle (Zhou, Wilson, and Dani, 2002). In line with broad ACh projections, nAChRs have been observed in many areas throughout the brain, and this distribution seems to be conserved across mammalian species (Millar and Gotti, 2009). Various methods, including mRNA analysis (Azam et al, 2002; Han et al., 2000; Schroder et al., 2001), positron emission tomography (PET) (Kimes et al., 2003; Rueter et al., 2006; Toyohara et al., 2009), and immunoprecipitation / toxin binding (Wooltorton et al 2003) have mapped the differential distribution of nAChR subtypes in the CNS. The α7 nAChR has been located in frontal and temporal cortices, the enthorinal cortex and subiculum, as well as distributed in the hippocampus, caudate, putamen, cerebellum, and in the midbrain. The α4β2 nAChR has also been found in these areas as well as in the parietal cortex and shows high expression in the midbrain (Hurst, Rollema, and Bertrand, 2013).

Although traditional views of cholinergic neuromodulation involve a diffuse, "volume transmission hypothesis" interpretation of nAChR activity, recent evidence has shown that post-synaptic nAChRs, and their activation by phasic, fast transient signalling, may be crucial for normal cognitive functioning (Sarter, Parikh, and Howe, 2009). NAChR mediated synaptic response has been shown in medial prefrontal cortex (mPFC) (Parikh et al, 2007), hippocampus (Hefft, Hulo and Bertrand, 1999), and VTA (Mameli-Engvall et al, 2006), and these synapses are likely important for attention (Poorthuis and

Mansvelder, 2013), memory (McGehee, 2002), and dopamine-dependant behaviour (Grace, Floresco, and Lodge, 2007), respectively. Thus, the effect of nicotine at post-synaptic nAChRs has the potential to modulate cognition at many regions and across cognitive domains.

1.2.2.3 nAChRs in Hippocampus, Cortex, Thalamus, and Mesolimbic DA System

The hippocampus receives endogenous cholinergic stimulation via the medial septum-diagonal band complex (Dutar et al, 1995), whose fibers synapse onto pyramidal cells, granule cells, interneurons, and mossy fiber terminals of the hilus (Frotscher, 1985). These afferents also provide high levels of nonsynaptic volume transmission throughout the hippocampus (Descarries, Gisiger, and Steriade, 1997). The highest density of hippocampal nAChRs are expressed on GABAergic interneurons and activation of these receptors promote neurotrasmitter release, with the α7 type nAChR being the predominant mediator of GABA cell depolarization (Alkondon et al, 1997). NAChR-induced GABA activation has been shown to inhibit hippocampal pyramidal neurons in rodents and this mechanism can prevent induction of LTP (Ji and Dani, 2000). NAChRs present on hippocampal glutamatergic neurons can also influence synaptic plasticity and lead to either LTP or long-term depression (LTD) depending on the synchrony of pre and post synaptic activation (Ji, Lape and Dani, 2001; Ge and Dani, 2005). The influence of hippocampal nAChRs on cognitive processing has been demonstrated in animal models, where cholinergic modulation of hippocampal neurons in rats has been shown to influence auditory sensory gating (Luntz-Leybman, Bickford, and Freedman, 1992).

The cortex receives cholinergic innervations from basal forebrain nuclei (Woolf, 1991). Both α7 and α4β2 type nAChRs modulate GABAergic inhibition of cortical interneurons, with the α4β2 type being the predominant modulator, and can result in either inhibition or disinhibition of cortical pyramidal neurons (Alkondon and Albuquerque, 2004). Unlike the hippocampus, where low affinity α7 type nAChRs act as the principle GABA cell modulator, the predominance of high affinity α4β2 nAChRs located on cortical GABA interneurons suggests that cortical signalling is more susceptible to both ACh volume transmission as well as exogenous agonists such as nicotine. The precise mechanisms underlying cholinergic activation of both cortical and hippocampal GABAergic interneurons is complex, and is dependant on GABA neuron subtype, as well as differential effects of nAChR and muscarinic receptor (mAChR) activation (Lawrence, 2008). However, cortical nAChRs have been specifically implicated in cognitive processes such as attention (Guillem et al, 2011), and thalamocortical glutamatergic transmission, an important pathway in cognition, is mediated by nAChRs (Poorthuis et al, 2009). Primates have a particularly high expression of α7 type nAChRs in the interneurons of the thalamic reticular nucleus, which has been interpreted to allow greater inhibitory control over sensory input to the cortex (Miwa, Freedman, and Lester, 2011).

Large cholinergic interneurons provide very dense cholinergic innervation of midbrain DA neurons (Zhou, Wilson, and Dani, 2002), via both synaptic and volume transmission (de Rover et al, 2002; Koos and Tepper, 2002) and heavily modulate DA activity in the striatum. Midbrain DA and GABAergic neurons express various types of nAChRs, including α4β2 and α7 types, with β2 containing receptors being the most predominant (Klink et al, 2001). Nicotinic activation of presynaptic VTA nAChRs enhances glutamate

inputs to DA neurons, and can induce LTP (Mansvelder and McGehee, 2000), and this mechanism is likely a major component in the formation of smoking addiction. Nicotine levels obtained via cigarette smoking slowly desensitize α4β2 type receptors which control GABAergic inhibition to DA neurons, but not low-affinity presynaptic α7 type nAChRs at glutamate synapses, and thus continuous smoking allows for increased burst-firing of disinhibited midbrain DA neurons at striatal reward areas such as the nucleus accumbens, thereby magnifying the reinforcing effects of the nicotine (Mansvelder and McGehee, 2002).

1.2.2.4. Nicotine actions at nAChRs

While both nicotine and ACh are agonists of nAChRs, it is important to consider that the actions of nicotine on brain cholinergic systems do not simply "mimic" that of endogenous ACh. Most cholinergic signalling in the brain is conjoint with high amounts of acetylcholinesterase, which can hydrolyze ACh at an extremely fast rate (Miwa, Freedman, and Lester, 2011). Because nicotine is not hydrolyzed by acetylcholinesterase, its actions at cholinergic receptor densities are much more sustained, allowing for the above described desensitization of high-affinity nAChRs. Furthermore, the membrane permeability of nicotine (Putney and Borzelleca, 1971) allows chronic nicotine exposure to upregulate nAChRs in cortex, midbrain, hippocampus, and hypothalamus (Marks et al, 1992; Nashmi et al, 2007), through selective pharmacological chaperoning of acetylcholine receptor and stoichiometry (SePhaChARNS; Lester et al, 2009). This upregulation magnifies the effects of nAChR activation and desensitization, both of

which contribute to nicotine's effects on cognition, addiction, and mood (Picciotto et al, 2008).

1.3. Cholinergic control of cognition

The diffuse and near-ubiquitous influence of the brain's cholinergic system makes it difficult to ascribe a specific function to cholinergic activation. However, behavioural, pharmacological and neuroimaging studies in both humans and animals have shed light on consistent overall themes pertaining to the effects of cholinergic modulation on cognition (Bentley, Driver and Dolan, 2011). In general, the cholinergic system acts to favour incoming "bottom up" processing of sensory stimuli, while suppressing "top down" influences. This may reflect a shift from an internalized default mode network to an active state suited for exogenous processing. A second theme involves the modulation of cognitive processing and neural activation by the cholinergic system in an "inverted U" fashion, with optimal levels of ACh resulting in optimal cognitive performance, and with deviations from this optimum, as either an increase or decrease in ACh, resulting in sub-optimal cognition. This mode of action mirrors that of DA, which also shows inverted-U type modulation of cognition, and is itself modulated by midbrain cholinergic activation (Jasinka et al, 2014). Together, these findings have implications for clinical populations marked by cognitive deficit who may benefit from pro-cholinergic treatment.

1.3.1. Cholinergic modulation of "Bottom Up" vs. "Top Down" processing

In order to efficiently process sensory information, a mechanism to shift between the incoming thalamo-cortico input to cortical layer IV (bottom up), and cortico-cortico communication between cortical layers (top-down) is required. ACh plays a central role, by limiting the spread of cortico-cortico excitation during sensory input, primarily through cholinergic activation of mAChRs (Kimura, Fukunda, and Tsumoto, 1999). Simultaneously, the sensory input signal is strengthened via nAChR activation on thalamicortical axons, enhancing excitability (Kawai et al, 2007). Through this mechanism, it is thought that the cholinergic system modulates the sensory signal-to-noise ratio, favouring feed-forward, stimulus dependent, rather than feedback, context dependent, processing (Roberts et al, 2005). As a result, cholinergic activation improves stimulus detection, particularly under taxing attentional conditions, where focus on a target stimulus is made difficult in the presence of noise and/or distractors (Sarter, Givens, and Bruno, 2001). Similarly, ACh levels are inversely correlated with cue-validity in a Posner spatial-attention paradigm (Phillips et al, 2000), suggesting that an increase in ACh represents attentional effort exerted when top-down, cue-dependent strategies are unreliable. The theme of ACh-modulated feed-forward processing may also occur at the level of the hippocampus, evidenced by observations that ACh improves memory encoding, but not consolidation (Hasselmo, 1999) and degrades memory if an ACh increase occurs after encoding (Bunce et al, 2004). Cholinergic activation of hippocampal interneurons is also crucial for gating of redundant stimuli (Luntz-Leybman, 1992). Thus it seems that the cholinergic system is highly specialized for processing of early, stimulus-driven bottom-up sensory inputs. Neuroimaging studies have shown suppression of fronto-parietal-temporal regions via pro-cholinergic treatments, including

nicotine, in regions associated with the so-called default mode network (Tanabe et al, 2011). It is possible that the cholinergic system acts as a neurochemical switch between an internalized state and one optimized for receiving sensory inputs. Failure to deactivate the default mode network has been proposed as a source of cognitive dysfunction in schizophrenia (Pomarol-Clotet et al, 2008), and interestingly, an α7 nAChR agonist has been shown to reduce activation in default mode network-associated areas (Tregellas et al, 2011).

1.3.2. "Inverted U" actions of the cholinergic system

Microdialysis experiments in animals have consistently shown that ACh release is positively correlated with attentional demand and/or task difficulty (Pepeu et al, 2004). Neuroimaging studies in humans show a similar trend, where pro-cholinergic drugs increase frontoparietal (Kumari et al, 2003; Bentley et al; 2004; Furey et al, 2008; Thiel et al, 2005) sensory (Hahn et al, 2007) and hippocampal (Kukolja, Thiel, and Fink, 2009) activity most robustly under task conditions with low cognitive demand. Similarly, activation of these areas is decreased relative to placebo by pro-cholinergic drugs during task conditions with high cognitive demands (Furey et al, 2000; Silver et al, 2008). Presumably, this reflects a lack of endogenous ACh-driven neural activation during low-demand tasks, allowing for the effects exogenous cholinergic stimulation to exert a greater influence, which is more robustly observed with neuroimaging. Highly-demanding tasks drive endogenous ACh release, thus limiting the effects of pro-

cholinergic drugs under these conditions, which may even act as detrimental to performance, depending on baseline cognitive ability (Bentley, Driver and Dolan, 2011). This inverted-U relationship between cholinergic activation and cognition is supported by the effects of pro-cholinergic drugs in individuals with sub-optimal cognition. In a neuropsychological test battery, Knott and colleagues (2015) showed improvements of working memory, verbal learning, verbal memory, processing speed, and executive function via 5'-diphosphocholine (CDP-choline), an α7 nAChR agonist, in healthy individuals with low baseline (placebo) cognitive performance, and this same study showed diminished cognition in individuals with high baseline performance. Procholinergic drugs have also been shown to normalize abnormal baseline neural activation due to sleep deprivation (Chuah et al, 2008), aging (Ricciardi et al, 2009), Alzheimer's Disease (AD) (Blin et al, 1997; Goekoop et al, 2006), and SZ (Jacobsen et al, 2004). Behavioural measures in AD and SZ patient groups have shown performance improvement via procholinergic drugs on demanding cognitive tasks, while the same drugs impaired performance in healthy controls (Bentley, Driver, and Dolan, 2008; Jacobsen et al, 2004). Similarly, nicotine studies have consistently shown cognitive improvement via nicotine administration to be inversely correlated with baseline performance (Ernst et al, 2001; Thiel, Zilles, and Fink, 2005) and positively correlated with task difficulty (Newhouse, Potter, and Singh, 2004). Overall these studies support the use of pro-cholinergic treatments as a means of improving cognition in populations suffering from cognitive deficits.

1.3.3. Cholinergic modulation of DA dependent cognition

While nAChRs located in cortical, thalamic, and hippocampal regions seem to influence cognition directly, their presence on midbrain VTA DA neurons, as discussed above, have implications for DA-driven modulation of both addiction and cognition. Activation of VTA DA neuron nAChRs leads to DA release at both mesolimbic (Tuesta et al, 2011) and mesocortical terminals (Rao et al, 2003). As such, it has been suggested that nicotine plays a dual role in the brain, namely; i) the induction and reinforcement of nicotine addiction by activation of the dopaminergic mesolimbic pathway, and ii) the modulation of cognition via direct actions on nAChRs as well as facilitating DA release in the prefrontal cortex (PFC) (Jasinka et al, 2014). The PFC is highly associated with cognition, and in particular, working memory performance, and it has been shown that PFC-dependent working memory is modulated by DA (Arnsten, 1998).

Interestingly, the effect of DA in the PFC obeys a similar inverted-U pattern of response as does ACh (Cools and D'Esposito, 2011), with deficient or excessive levels of DA resulting in sub-optimal working memory (Cools et al, 2009). Moreover, the baseline-dependency of DA's effect on cognition seems to reflect modulation of connectivity between PFC and striatum (Cools and D'Esposito, 2011), both which are areas that receive increased dopamine release in response to nicotine's actions at the VTA (Livingstone et al, 2009; Rice and Cragg, 2004). Furthermore, SZ, which is characterized by marked cognitive deficits (Gold and Harvey, 1993), is associated with both nicotine receptor dysfunction (Leonard et al, 1996), as well as reduced PFC activity, which is predicted by exaggerated striatal DA function (Meyer-Lindenberg, 2002). Thus, the cholinergic system has the ability to modulate cognition both directly, through activation

of nAChRs within key brain areas, as well as indirectly, through activation of the DA system, and this may have robust implications for clinical syndromes characterized by cognitive dysfunction, such as SZ.

1.4.0. Smoking and Schizophrenia

Tobacco use among SZ patients is remarkably high, with 70-80% of patients being smokers, compared to 20-30% of the general population (Ziedonis et al, 2008). Moreover, where most chronic smokers tend to carefully titrate a precise nicotine dose desired from each cigarette, smokers with schizophrenia tend to maximize nicotine yields when smoking, by inhaling more deeply, using a higher puff-rate, and holding more smoke in their lungs (Tidey et al, 2005). In light of these observations, research into nicotine's effects in SZ has given rise to the self-medication hypothesis (Kumari and Postma, 2005), which attributes patients' smoking habits to reduction of positive, negative, and cognitive symptoms by counteracting underlying neurobiological deficits.

1.4.1. Cholinergic dysfunction in schizophrenia

Several lines of evidence point towards a dysfunction in cholinergic signalling within the brains of SZ patients (D'Souza and Markou, 2012). Choline acetyltransferase, an enzyme responsible for the synthesis of ACh, was shown to be decreased in the nucleus accumbens (Bird et al, 1977) and pons (Karson et al, 1993) of post-mortem SZ brains relative to controls. Another post-mortem analysis reported increased numbers of

cholinergic neurons in the pedunculopontine nucleus in SZ (Garcia-Rill et al, 1995). In vivo imaging studies have shown increased choline levels in the left caudate nucleus (Bustillo et al, 2002) of SZ patients compared to controls, and analysis of untreated first episode SZ patients found a positive correlation between psychosis duration and choline levels in the thalamus and left anterior cingulate (Théberge et al, 2004).

Alpha-bungarotoxin, a compound found in snake venom with high affinity for α7 nAChRs, has been used to indentify nAChRs in post-mortem SZ brains, and reduced binding has been reported in the thalamic reticular nucleus (Court et al, 1999) and hippocampus (Freedman et al, 1995). α7 nAChR antibodies have also been used, and reduced binding using this method was shown in the PFC of SZ post-mortem tissue (Guan et al, 1999). Endogenous α7 nAChR autoantibodies have also been identified in some SZ patients (Chandley et al, 2009). Post-mortem studies using radioligands have shown reduced expression of α4β2 nAChRs in hippocampus, cortex, and caudate (Breese et al, 2000) as well as striatum (Durany et al, 2000) in SZ brains relative to controls. Single nucleotide polymorphisms in the neuregulin-1 gene, which regulates the expression of α7 nAChRs, were shown to reduce α7 nAChR mRNA in the dorsolateral PFC, and this effect was more pronounced in SZ patients compared to controls (Matthew et al, 2007). Overall, these studies suggest a strong association between SZ and abnormal cholinergic function, a state which is likely to contribute to irregularities in other neural systems.

1.4.2 The NMDA / nAChR link in schizophrenia

The modern glutamate hypothesis of SZ arose following the observation that drugs which antagonize NMDARs, such as phencyclidine (PCP) and ketamine, induce symptoms similar to positive, negative, and cognitive symptoms in SZ (Moghaddam and Javitt, 2011). This was in contrast to dopamine agonists, such as amphetamines, which could emulate positive symptoms but not negative or cognitive symptoms (Javitt and Zukin, 1991), as well as the realization that most first and second generation antipsychotics fail to ameliorate cognitive symptoms (Hill et al, 2010). Thus, much of the current research in SZ has focused on NMDAR hypofunction in key areas such as the PFC and hippocampus (Gilmour et al, 2012).

Interestingly, recent animal models have revealed important relationships between α7 nAChRs and NMDAR function. A study in primates demonstrated that α7 nAChRs are essential for normal functioning of NMDAR mediated cognitive circuits in the dorsolateral PFC (Yang et al, 2013). Mice with genetic microdeletions of α7 nAChRs showed decreased NMDAR expression and glutamatergic synapse formation (Lin et al, 2014). NMDAR antagonist-induced object recognition deficits in rats have been reversed via systemic nicotine (Jacklin et al, 2012), and conversely, nicotine-induced enhancement of gamma oscillations in rat hippocampal slices were completely blocked by the NMDA receptor antagonist D-AP5 (Wang et al, 2015). Thus, it seems that nAChRs and NMDARs enact "metamodulation" (Katz and Edwards, 1990), meaning that both receptor types influence each other in the modulation of neurotransmission and cognition (Marchi, Pittaluga, and Grilli, 2014). Therefore, smoking behaviour in SZ may reflect an attempt to normalize neuromodulatory abnormalities as predicted by the glutamate hypothesis, and which arise from dysfunction at nAChR and NMDA dependant synapses.

1.4.3 Cognition in schizophrenia

The observation that current medications do little to improve cognition in SZ (Hill et al, 2010) is troubling, since cognitive deficit has been described as the core of the disorder (Elvevag and Goldberg, 2000). Cognitive deficits appear before evidence of psychosis and tend to also be present in unaffected relatives of SZ patients (Heydebrand, 2006) as well as first episode SZ patients (Snitz, MacDonald, and Carter, 2006). For this reason, core cognitive deficits are being explored as potential endophenotypes for SZ, and may be valuable targets for diagnostics and treatment (Gur et al, 2007). Cognitive improvement in SZ is also strongly associated with functional outcome (Green, Kern, and Heaton, 2004), including employment (McGurk et al, 2003), independent living (Leung et al, 2008), quality of life (Brekke et al, 2001) and relapse prevention (Jeste et al, 2003), underlining the importance of developing pro-cognitive treatment for patients. In consequence, a large scale initiative, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS; Marder and Fenton, 2004), was launched in order to respond to this need. While nicotine has been reported to improve cognition in SZ (Barr et al, 2008), the health consequences of smoking has necessitated the need for non-nicotine agonists of nAChRs. The α7 nAChR is an identified target of this initiative, and so far, synthetic α7 agonists have shown promising results in animal models, with improvements of episodic memory, working memory, and attention (Wallace and Porter, 2011). Unfortunately, novel agents which have proven safe and effective in animal models have a 95-97% drug registry failure rate (Hurko, 2010),

suggesting that animal models are still far from achieving a 1:1 translational accuracy and may only capture minute aspects of cognitive dysfunction in SZ (Hagan and Jones, 2005). Furthermore, due to the high costs and time investment of preclinical and clinical trials during development of novel SZ treatments, there is a crucial need for techniques which provide reliable data on whether a candidate drug or treatment will proceed to yield successful cognitive improvements (Breier, 2005). One promising approach to this end involves the identification of neurophysiological biomarkers in SZ.

1.4.4. Biomarkers in schizophrenia

Due to the heterogeneity of symptoms in SZ (Arango, Kirkpatrick, and Buchanan, 2014), the identification of biomarkers and subsequent targeting of genetically determined endophenotypes is an effective approach in developing novel treatment strategies. Endophenotypes are defined as a subset of biomarkers which meet the following criteria: 1) they are associated with an illness and exhibit deficits in patients; 2) they are stable over time; 3) they are relatively independent of fluctuations in clinical symptoms; 4) their related deficits are present (often to a lesser degree) in genetically related family members; and 5) they are heritable (Light et al, 2012). While biomarkers and endophenotypes are often interpreted to represent a specific brain dysfunction, it is often useful to consider that a given biomarker may actually indicate intact neural resources, the functions of which are attenuated in illness (Light et al, 2015). Using this approach, it also follows that any improvement in a given biomarker through pharmacological challenge, such as the improvement of cognitive traits in SZ via nicotine, should signal

that these attenuated neural functions can be rescued, and that the corresponding pharmacological avenue should be pursued as a target for therapeutic intervention.

1.5. EEG and ERPs in cognition and SZ

Electroencephalography (EEG) and ERP techniques have been found to be particularly well suited in revealing biomarkers of SZ (Luck et al, 2011). These methods provide a direct measure of electrical activity during neurotransmission, and they are relatively inexpensive, allowing for large, multi-site studies to be carried out (Hesselbrock et al, 2001). Several ERP components have analogs in animal models allowing for translational research (Woodman, 2012), and many ERPs are supported by decades of research establishing their sensitivity and test-retest reliability (Bramon et al, 2004). Furthermore, the high temporal resolution of ERPs allows for assessment of early neural oscillations with millisecond precision, such as those involved in the "bottom up" processing of external stimuli controlled via cholinergic signalling (Roberts et al, 2005). Over the past decades, a multitude of EEG and ERP studies have investigated the effect of nicotine and other cholinergic agonists on cognition in both healthy controls and SZ.

1.5.1 P50 and sensory gating

Dysfunction in gating of the preattentive auditory P50 ERP was among the first discovered biomarkers of so-called hypervigilance in SZ. In a landmark paper, Adler and colleagues (1982), described "neurophysiological evidence for a defect in neuronal

mechanisms involved in sensory gating in schizophrenia". This simple paradigm utilizes two short (~1ms), identical sounds, delivered sequentially with ~500 ms interstimulus intervals. The P50 is a positive-polarity component which occurs approximately 50 s post-stimulus. The first stimulus, known as the conditioning stimulus, or S1, is theorized to activate sensory pyramidal neurons simultaneously with feedback inhibitory GABAergic neural circuits which inhibit the neural response to the second stimulus, known as the test stimulus, or S2 (Nagamoto et al, 1989). Amplitudes of S1 and S2 are typically compared using either the ratio (rP50, S2/S1) or difference (dP50, S1-S2) method, and indexing of sensory gating using these methods has consistently shown reductions in SZ compared to healthy controls (Patterson et al, 2008). Interestingly, nicotine has been shown to normalize deficient P50 gating in both SZ patients as well as their unaffected genetic relatives (Adler et al, 1992). Improvement in P50 gating has also been shown following administration of α7 nAChR agonists in SZ (Freedman, 2014) as well as healthy controls stratified for low-baseline gating (Knott et al, 2014c). The P50 paradigm is discussed in detail in Chapter 2.

1.5.2 MMN and acoustic change detection

MMN is also a preattentive ERP component, generally considered as an index of early processing of acoustic change (Näätänen et al, 2007), and MMN deficiency has been described as a breakthrough biomarker in predicting psychosis onset (Näätänen et al, 2015). The MMN is traditionally elicited as a negative ERP component, occurring ~150 ms post-stimulus, observed as a difference waveform obtained by subtracting the ERP

elicited from "deviant" sounds from those of a "standard" sound. The standard is usually a sinusoidal tone, and each deviant is a variation on the standard soundwave. For example, in the "optimal" MMN paradigm (Näätänen et al, 2004), 5 deviants are used, which differ from the standard in pitch, loudness, aural location, duration, and continuity (where a silent "gap" appears mid-tone). MMN deficiencies, and particularly duration deviant amplitudes, have been well documented in SZ (Näätänen et al, 2009), and these deficits are highly associated with functional impairments, with a reliability comparable to, or even exceeding, neuropsychological tests over 1 year (Light and Braff, 2014). Nicotine has been shown to increase MMN amplitude in both smokers and nonsmokers (Harkrider and Hedrick, 2005), as well as smoking SZ patients (Dulude et al 2010), but not nonsmoking SZ patients (Inami et al, 2007). Interestingly, in one study, MMN amplitude improvement by nicotine correlated with nicotine-induced improvement (inhibition) of SZ patients' hallucinations (Fisher et al, 2012). The MMN paradigm is discussed in detail in Chapter 3.

1.5.3 P300 and attention

The P300 is comprised of two different positive-polarity ERPs elicited approximately 300 ms post-stimulus. First, the fronto-central P3a (also known as the novelty P300 if elicited in response to novel stimuli), has been proposed to reflect redirection of attention towards novel, distracting sounds (Escera et al., 1998; Friedman et al., 2001), as well as broader alerting (SanMiguel et al., 2010) and executive control (Escera and Corral, 2007) function. Second, the parietal P3b, which is elicited during target stimulus detection

(Polich, 2007). Both P3a and P3b are deficient in SZ, and their attenuation has been shown to be related to symptom severity (Mathalon, Ford, and Pfefferbaum, 2000). P3a has also shown high stability in SZ patients over a one year retest interval (Light et al, 2012). Chronic smokers show reduced P3b amplitudes compared to nonsmokers (Hedges and Bennett, 2014), and smoking withdrawal further reduces P3b amplitudes (Evans et al, 2013), while acute smoking increases both P3a and P3b amplitude (Polich and Criado, 2006). A recent study showed nicotine to modulate P3a and P3b in nonsmokers in an inverted-U fashion based on baseline P3a and P3b amplitudes (Knott et al, 2014b). The P300 paradigm is discussed in detail in chapter 4.

1.5.4 Resting-state EEG and arousal

Neural activity can also be quantified using EEG in the absence of an external stimulus. Distinct frequency oscillations measured at the scalp have been shown to reflect the summed activity of several large-scale brain networks, including influence from cortical and sub-cortical structures (Mantini et al, 2007). While it is unlikely that any one frequency band is a reflection of any single aspect of cognition, numerous studies spanning many decades have strongly implicated certain oscillations with a number of cognitive processes (Hermann et al, 2015). Alpha oscillations are predominantly observed in adults at rest with eyes closed (Simon and Emmons, 1956) and are associated with memory (Klimesch, 1997), attention (Hanslmayr et al, 2011) as well as top-down directed inhibitory control (Klimesch et al, 2007). The Beta frequency is associated with cognitive processes responsible for maintenance of cognitive control and attentional

effort (Kilavik et al, 2013; Stoll et al, 2015). Delta oscillations have been associated with inhibition of thalamocortical inputs by the frontal cortex during attention (Harmony, 2013). The theta frequency band is associated with hippocampus-dependant memory (Klimesch, 1999; Mitchell et al, 2008) as well as frontal cortex-dependent inhibition (Huster et al, 2013). Gamma oscillations have been proposed to reflect general activation of cortical tissue, non-specific to any cognitive function (Merker, 2013). Abnormal EEG synchrony has been observed in SZ patients, including increased delta and theta amplitudes (Narayanan et al, 2014), however, these findings were not replicated in first-episode patients, suggesting that abnormal EEG may be more strongly associated with symptoms of SZ as opposed to underlying genetic characteristics (Ranlund et al, 2014).

In smokers, nicotine has consistently shown reduction of slow wave (delta and theta) activity, as well as increases in fast wave (alpha and beta) activity (Knott, 2001). Nonsmokers have shown increases in alpha activity, but not decreases in slow waves (Fisher et al, 2012), suggesting that alpha activity is modulated by activation of nAChRs, whereas delta and theta activity is altered as a result of smoking withdrawal. Resting state EEG is discussed in detail in chapter 5.

1.6. Monoamine Oxidase and smoking: are we missing half the story?

As detailed in the above sections, the literature pertaining to nicotine and its effects on the brain, cognition, addiction, and mental illness, is expansive. However, it is somewhat remarkable that the vast majority of research tends to view tobacco smoking as little more than a vehicle through which nicotine is delivered to the brain. It is now understood that

tobacco smoke contains approximately 4700 components (Borgerding and Klus, 2005), some of which act as potent MAO inhibitors in humans (Lewis, Miller, and Lea, 2007). MAO inhibition can have a robust effect on neurotransmitter activity (Meyer et al, 2006) and thus likely contributes to the cognitive effects associated with tobacco use. Presently, studies aimed to specifically assess the effect of MAO inhibition on cognition are scarce, and studies examining MAO inhibition and nicotine in relation to cognitive biomarkers of SZ are so far non-existent. Therefore it is essential to understand the degree to which MAO inhibition contributes to the psychopharmacological effects of smoking normally associated with nicotine.

1.6.1 MAO function and localization

MAO, originally identified in the liver as tyramine oxidase (Hare, 1928) is a flavin adenosine dinucleotide-containing enzyme (flavoenzyme) located on mitochondrial outer membranes in the brain and peripheral tissues, which oxidizes neurotrasmitter amines, as well as other endogenous and exogenous amines (Finberg, 2014). Two isoforms of MAO exist in humans; MAO-A and MAO-B, which are both encoded by genes on the short arm of the X chromosome, and which exhibit ~60% sequence homology (Chen, 2004). The two isoforms of MAO are differentiated by their inhibitors and their substrates. Specifically, MAO-A is inhibited by clorgyline and oxidizes endogenous neurotransmitters such as 5-HT as well as NA, while MAO-B is inhibited by L-deprenyl and preferentially oxidizes exogenous amines such as phenylethylamine (Finberg, 2014; Johnston, 1968; Knoll and Magyar, 1972). The substrate specificities of each MAO

isoform are relative, meaning that MAO-A will oxidize MAO-B substrates at high monoamine concentrations, and vice-versa. DA is oxidized equally by both MAO-A and MAO-B at similar concentrations.

While controversy exists over the precise localization of MAO isoforms in the brain, immunohistochemistry and enzyme histochemistry experiments have provided some consistent observations (Finberg, 2014). Varying levels of both isoforms are found throughout the brain, and in general, MAO-A is expressed in noradrenergic cell bodies of the locus coeruleus, and MAO-B is expressed in glia, ependyma, and in serotonergic cell bodies of the raphe nucleus (Youdim and Finberg, 1991). There is evidence that 5-HT is metabolized by MAO-A in raphe nuclei projection areas, such as the hypothalamus (Fagervall and Ross, 1986), and DA is metabolized by MAO-A in substantia nigra projection areas, such as the striatum (Wachtel and Abercrombie, 1994).

In general, the majority of MAO's actions occur within neurotransmitter-containing varicosities, where monoamine neurotransmitters are transported into vesicles via vesicular monoamine transporters (VMAT). Vesicular transport is an ongoing, dynamic process, and free monoamine neurotransmitters in the cytoplasm exist in dynamic equilibrium with those stores in vesicles, where there is minor but continuous outward leakage (Eisenhofer et al, 2004). Therefore, the major function of MAO in a presynaptic neuron is to metabolize extra-vesicular neurotransmitters, thereby maintaining the balance of intra- and extra-vesicular neurotransmitter, a state which is in constant flux as synaptic transmitters re-enter the presynaptic cell via reuptake transporters, e.g. dopamine transporter (DAT), norepinephrine transporter (NET) and 5-HT transporter (SERT). MAO functions similarly in the postsynaptic neuron, where catechol O-methyltransferase

(COMT) and aldehyde metabolizing enzymes also take part in monoamine neurotransmitter metabolism (Kopin, 1985).

1.6.2 Effect of MAO inhibition

The net effect of MAO inhibition is an increase in synaptic levels of neurotransmitters, mainly due to an increase in vesicular storage capacity potentiated by increased neurotransmitters in the cytoplasm (Buu et al, 1989). The increased cytoplasmic monoamine levels in turn potentiate compensatory mechanisms, such as downregulation of neurotransmitter-synthesizing enzymes (Pothos et al, 1998) and an increase in the synthesis of MAO itself (Rendu et al, 2011). Other enzymes which are inhibited in a feedback-fashion by the presence of monoamine neurotransmitters, such as tyrosine hydroxylase and tryptophan hydroxylase, are thus affected by MAO inhibition, as increased cytoplasmic catecholamine presence causes a down-regulation of these synthesizing enzymes (Daubner et al, 2011).

1.6.3 Pharmacological inhibition of MAO

The finding that MAO inhibition increases synaptic neurotransmitters led to great clinical interest in the use of MAO inhibitors as pharmacotherapeutics (Youdim, Edmondson, and Tipton, 2006). The first MAO inhibitors, developed for treatment of depression, were non-selective and irreversible, and were thus associated with highly dangerous side-effects, such as a rare but potentially deadly hypertension known as the "cheese effect",

which occurs when patients taking irreversible MAO inhibitors ingest tyramine-containing foods (such as cheese), which potentiates sympathetic cardiovascular activity by releasing NA. The development of reversible and selective MAO inhibitors, such as moclobemide, which selectively and reversibly inhibits MAO-A, allowed for safer prescription of this class of antidepressant (Da Prada et al, 1988). Reversible MAO-A inhibition has been shown to be particularly effective in the treatment of depression in elderly patients (Gareri et al, 2000) as well as atypical depression characterized by hysteria, hypersomnia, bulimia, tiredness, and impression of rejection (Zisook, 1985). MAO inhibition has also been used in the treatment of Parkinson's disease (Youdim and Bakhle, 2006), Alzheimer's disease (Riederer, Danielczyk, and Grunblatt, 2004), and interestingly, smoking cessation (Berlin, 1995).

1.6.4 Inhibition of MAO by tobacco smoke

It is now known that chronic smoking leads to robust inhibition of both MAO-A and MAO-B in the brain, as well as the lung, kidneys, spleen, and other peripheral tissues and organs (Fowler et al, 2005). PET studies have revealed reductions in brain MAO-A by ~28% (Fowler et al, 1996_a) and MAO-B by ~40% (Fowler et al, 1996_b) in chronic smokers, though a more recent study showed ~60% inhibition of MAO-A in chronic smokers compared to healthy controls (Leroy et al, 2009). Although nicotine does cause weak inhibition of MAO, this only occurs at levels comparable to two thousand times those which are observed in chronic smokers, and thus nicotine is not likely the source of MAO inhibition in smoking humans (Lewis, Miller, and Lea, 2007). Other constituents of

tobacco smoke, such as the β-carboline alkaloids norharman and harman, have been shown to be potent inhibitors of MAO-A and MAO-B (Herraiz and Chaparro, 2005), and plasma levels of these compounds are inversely correlated with PET-measured levels of MAO binding during chronic smoking and acute withdrawal (Bacher et al, 2011). Interestingly, while MAO activity has been shown to increase within 8 hours of smoking abstinence, the effects of smoking-related upregulation of MAO-synthesis has been estimated to last as long as 20 years (Rendu et al, 2011), suggesting that at least some of the withdrawal effects associated with smoking cessation could be extremely long-lasting.

1.6.5 MAO and ERP-indexed cognition

While MAO activity has been associated with global traits such as aggression (Alia-Klein et al, 2008), depression (Meyer et al, 2006), and personality (Tochigi et al, 2006), little is known about MAO's influence on early cognitive processing. Evidence of a potential influence of MAO inhibition on cognition stems from studies involving the modulation of MAO substrates on event-related potentials.

Modulation of dopamine via dextroamphetamine disrupted P50 gating (Light et al, 1999), and dopamine D2 receptor antagonism altered P50 gating and P300 amplitudes in an inverted-U fashion depending on baseline performance (Csomor et al, 2008; Takeshita and Ogura, 1994). 5-HT selective reuptake inhibition has been shown to decrease P50 gating (Oranje et al, 2011), and 5-HT depletion reduces P50 gating, but only when combined with depletion of dopamine (Mann et al, 2007). Modulation of 5-HT does not

influence P300 (Ahveninen et al, 2002), and neither DA nor 5-HT modulation seems to affect MMN (Leung et al, 2010). Modulation of NA has been shown to disrupt P50 gating (Adler et al, 2004), as well as P300 (Swick et al, 1994) but has no influence on MMN (Mervaala et al, 1993).

Because chronic tobacco smokers are routinely exposed to a state of MAO-inhibition and acute nicotine delivery, the degree to which these two pharmacological environments affect cognitive ERPs should be elucidated. As MAO inhibition increases monoamine neurotransmitter release, it is likely that nicotine's effects on cognitive processing may differ depending on the state of MAO inhibition. For example, it has been shown that the inverted-U actions of nicotine on P50 sensory gating varies depending on COMT polymorphisms (de la Salle et al, 2013), suggesting that intracellular neurotransmitter levels can play a role in the cognitive effects of nicotine. So far, the separate and combined effects of MAO inhibition and nicotine on early cognitive processing is not known.

1.7. Study rationale, research objectives, and hypotheses

The preceding review highlighted the effects of smoking on cognition, it's importance in SZ, and the contributions of both nicotine and MAO inhibition. A glaring hole in the current literature is the fact that research into nicotine and MAO inhibition has been kept separate, with little or no consideration given to the fact that both pharmacological factors are continuously at play in traditional tobacco smoking. Thus, an investigation into the

separate and combined effects of nicotine and MAO inhibition on cognition is long overdue.

A second limitation in the current literature on tobacco smoking is the use of smokers in studies of nicotine on cognition. While the ethical considerations of exposing nonsmoking individuals to tobacco smoke are obvious, the use of smokers in nicotine studies has prevented a distinction between true effects of tobacco constituents on cognition versus the alleviation of cognitive deficits associated with smoking withdrawal. Therefore, there is a need for studies designed to simulate the effects of tobacco smoke, with consideration given to both nicotine and MAO inhibition, in healthy, nonsmoking individuals, without exposing these individuals to the addicting and health-deteriorating risks of real tobacco smoke.

Finally, much of the research into smoking's effects in SZ has been confounded by patients' smoking status, as well as concurrent medications and/or treatments. This is due to the high prevalence of smoking in SZ, which makes it extremely difficult to recruit a sufficient sample size of patients who are nonsmokers, as well as the impracticality and ethical issues in delaying or stopping patients' treatment for the duration of a cognitive study. As such, in order to study the effects of nicotine and MAO inhibition in sub-optimal cognition, preliminary studies should target individuals on the lower-spectrum of cognition in the healthy population.

This thesis aims to address the above limitations by 1) studying early cognitive ERPs at baseline (placebo), as well as under conditions of acute nicotine, pharmacological inhibition of MAO, and the combination of both nicotine and MAO inhibition. 2) using healthy, nonsmoking individuals, while simulating the pharmacological environment of

tobacco smoke using nicotine gum and moclobemide, in order to limit potential health effects, and finally 3) stratifying participants based on baseline (placebo) ERP amplitudes, and targeting individuals at the lower end of the spectrum as a model of cognitive deficit in mental illness. Different aspects of cognition will be targeted using a test battery of EEG and ERP paradigms, as outlined in the following objectives.

1.7.1 Statement of research objectives

Research objective 1: To study the separate and combined effects of nicotine and MAO inhibition via moclobemide on sensory gating as indexed by the auditory P50 paradigm, in healthy individuals stratified for low and high baseline gating.

Hypothesis: It was hypothesized that both nicotine and moclobemide, when delivered separately, would modulate P50 gating in an inverted-U fashion, improving gating in participants who exhibited low gating at baseline, and diminishing gating in participants who exhibited high gating at baseline. It was further hypothesized that the combination of nicotine and moclobemide would further improve gating in low baseline participants, beyond the effects of either individual drug, and that the combination would also reverse gating detriments observed in the individual drug conditions in participants with high baseline gating.

Research objective 2: To study the separate and combined effects of nicotine and MAO inhibition via moclobemide on auditory change detection as indexed by the MMN paradigm, in healthy individuals stratified for low and high baseline MMN. (Chapter 2)

Hypothesis: It was hypothesized that nicotine would modulate MMN in an inverted U fashion, increasing amplitudes to MMN deviants in low-baseline individuals, while diminishing amplitudes to MMN deviants in high baseline individuals, and this effect would be most robust in the duration deviant. MAO inhibition was not expected to modulate MMN, and would not have an effect on nicotinic modulation of MMN in the combination condition.

Research objective 3: To study the separate and combined effects of nicotine and MAO inhibition via moclobemide on novelty detection and attention as indexed by the P3a and P3b auditory paradigm, in healthy individuals stratified for low and high baseline P3a and P3b amplitudes. (Chapter 3)

Hypothesis: It was hypothesized that both nicotine and moclobemide, when administered separately, would modulate P3a and P3b in an inverted U fashion, increasing amplitudes in low-baseline individuals, while diminishing amplitudes in high baseline individuals. The combination of moclobemide with nicotine was expected to increase both P3a and P3b amplitudes beyond the effect of either individual drug, with the opposite effect, i.e. diminished amplitudes, in high baseline individuals.

Research objective 4: To study the separate and combined effects of nicotine and MAO inhibition via moclobemide on arousal state as indexed by resting-state EEG. (Chapter 4)

Hypothesis: It was hypothesized that both nicotine and moclobemide, when administered separately, would increase power in the alpha frequency band. Nicotine, when combined with moclobemide, was expected to exhibit a more robust increase in alpha power, beyond the effects of either individual drug. It was also hypothesized that moclobemide would increase power in the theta frequency band, and that nicotine would increase this effect in the combination condition.

CHAPTER 2

The separate and combined effects of monoamine oxidase inhibition and nicotine on P50 sensory gating

2.1. Overview

This manuscript provides an investigation into the separate and combined effects of nicotine and moclobemide on P50 sensory gating, an ERP paradigm which indexes the brains ability to automatically gate out redundant auditory stimuli. The P50 is the earliest auditory ERP investigated in this thesis, occurring approximately 50 ms post-stimulus. P50 gating is especially relevant to both the nicotinic and monoaminergic systems, as they are both thought to influence different aspects of the paradigm, i.e. modulation of amplitude by dopamine and inhibition of the redundant sound by activation of nAChRs on GABAergic interneurons of the hippocampus. Thus the objective of this manuscript was to determine if the different aspects of smoking modeled in our experiment affect sensory gating in a manner predicted by the current literature. The 24 participants were stratified based on baseline gating performance in order to assess if the effects of each drug condition were baseline dependent.

2.2. Statement of author contribution

The initial experimental design of this study was drafted by Verner Knott and Pierre Blier, with input by Dylan Smith. Participants were recruited, screened and given orientations by Dylan Smith, with psychological and pharmacological screenings also performed by Vadim Ilivitsky. Programming of experimental stimuli was completed by Derek Fisher and Dylan Smith. ERP recording/analysis, statistical analysis, writing of the manuscript and generation of figures was completed by Dylan Smith. All authors critically reviewed and approved the final manuscript. This study was supported by a University of Ottawa Medical Research Fund grant awarded to Verner Knott.

2.3 Title page

The Separate and Combined Effects of Monoamine Oxidase A Inhibition and Nicotine on Sensory Gating of the P50 Event Related Potential

Dylan M Smith[1,2], B.Sc, Derek Fisher[3], Ph.D., Pierre Blier[1,2,4]MD, Vadim Illivitsky[4] MD, Verner Knott[1,2,4]Ph.D., C.Psych.

[1] University of Ottawa Institute of Mental Health Research, Ottawa, Ontario, Canada
[2] Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada
[3] Department of Psychology, Mount Saint Vincent University, Halifax, Nova Scotia, Canada
[4] Royal Ottawa Mental Health Centre, Ottawa, Ontario, Canada

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2.4 Abstract

Introduction: The cognitive effects of nicotine in humans remains a topic of great interest, due to the continued prevalence of cigarette smoking in society, as well as the hypothesis that cognitively impaired populations such as schizophrenia patients use nicotine as a means of self-medicating against deficits of sensory gating. However, chronic smoking can predispose individuals to robust monoamine oxidase (MAO) inhibition, and thus far, the effect of MAO inhibition on human sensory gating is unknown. *Methods:* In this study, we investigated the effects of both nicotine (6mg gum) and pharmacologically induced MAO-A inhibition via moclobemide (75mg) on P50 event-related-potential-indexed sensory gating in a sample of 24 healthy non-smoking males. *Results:* Ratio score (rP50) measured gating revealed significant improvement in auditory stimulus suppression after combined nicotine and MAO-A inhibition compared to placebo and to the nicotine-alone condition. This nicotine + MAO-A inhibition-induced efficient gating was consistent regardless of participants' baseline (placebo) gating efficiency, despite the observation that nicotine in the absence of MAO-A inhibition exhibited a detrimental effect on gating in participants with high baseline suppression ratios. *Conclusion:* Nicotine and monoamine oxidase-inhibiting agents in tobacco smoke appear to exert a synergistic effect on sensory gating, which may contribute to the elevated dependence rates seen in populations with cognitive deficits such as schizophrenia.

2.5 Introduction

While a large volume of research has focused on nicotine's effects on cognition in schizophrenia (Hashimoto et al. 2005), evidence suggests that the neuropsychopharmacological effects of tobacco smoke are not a result of nicotine's actions alone. A number of studies have demonstrated an inhibition of the enzyme monoamine oxidase (MAO) via tobacco smoke (Berlin et al, 1995; Fowler et al. 2003; Oreland et al. 1981) and moreover, this inhibition is likely not a result of nicotine (Castagnoli et al. 2002). MAO activity has been negatively correlated with smoking behaviour, and low baseline MAO significantly predicted the intensity of withdrawal symptoms after smoking cessation (Rose et al. 2001). It is thus probable that MAO inhibition plays a significant role in the reinforcing effects of smoking behaviour. Interestingly, pharmacologically inhibited MAO has been shown to antagonize the cognitive deficits associated with cholinergic blockade (Wesnes et al. 1989). As such, an understanding of the relationship between cognition, MAO activity, and nicotine is a necessary step on the path to understanding smoking behaviour, as well as achieving practical treatment of low-cognition, high-smoking populations.

Smoking rates among individuals with mental illness (40.1%) are double the rate reported in individuals with no psychiatric diagnosis (21.3%) (Lawrence et al. 2009). Schizophrenia patients, in particular, exhibit the highest rates of smoking; estimated to be as high as 80% (Dalack et al. 1999). This elevated smoking rate, combined with observed deficits in nicotinic receptors (nAChRs) in patients (Dalack et al. 1998) has led to the hypothesis that schizophrenia patients utilize smoking as form of self medication against

cognitive deficits that characterize the disease (Kumari and Postma, 2005). Specifically, smoking has been shown to normalize auditory event-related potential (P50) indexed sensory gating deficits in schizophrenia and 1st degree relatives (Adler et al. 1992 & 1993). However, the extent to which this effect results from nicotine, MAO inhibition, or the combination thereof, is not known.

Two isoforms of MAO exist in humans; MAO-A which preferentially metabolizes serotonin and norepinephrine and is preferentially inhibited by clorgyline and moclobemide, and MAO-B which catabolises phenylethylamine and benzylamine and is preferentially inhibited by L-deprenyl (selegiline). Dopamine, tyramine and tryptamine are metabolized by both MAO-A and MAO-B (Weyler et al, 1976; Johnston et al, 1968; Lewis et al, 2007, Yamada and Yasuhara, 2004). It has been suggested that MAO may act to maintain a low concentration of monoamine neurotransmitters within the neuron, thus facilitating the uptake of neurotransmitters from the synaptic cleft. MAO may also protect the neuron from accidental stimulation by extraneous amines (Saura et al. 1996), though it has been shown that the MAO-A inhibitor clorgyline inhibits serotonin degradation (Blier et al. 1986; Twist et al. 1990) suggesting MAO-A may oxidize serotonin exterior to the neuron (Shih et al. 1999).

In clinical settings, pharmacological MAO inhibition is typically used as treatment for depression, though it has also proven effective in Parkinson's and Alzheimer's diseases (Youdim et al. 2006). The potentially lethal side-effects of early irreversible MAO inhibitors earned these drugs a dangerous reputation, only to be used as a last resort (Youdim and Bakhle, 2006). The development of reversible MAO inhibitors, such as moclobemide, allowed for safe and effective clinical use of these medications,

aided in part by the observation that selective inhibition of either MAO-A or B increases dopamine release in striatum (Haefely et al, 1992). Moclobemide has been proposed as an effective aid for smoking cessation, possibly by counteracting the state of dopamine depletion experienced by ex-smokers as a result of normalizing MAO activity 3-4 weeks after quitting (Berlin et al., 1995; Watkins et al., 2000).

To our knowledge, the contribution of MAO inhibition to the cognitive effects of cigarette smoking, and specifically sensory gating, has not been studied. However, there is evidence that both dopaminergic and cholinergic mechanisms are simultaneously at play. Gating, typically measured electroencephalographically by comparing the P50 amplitude difference (dP50) or ratio (rP50) of two identical auditory stimuli ("clicks") presented 500 ms apart, was differentially improved by nicotine depending on dopamine transporter 1 (Millar et al, 2011) and D2 receptor (Knott et al, 2010) gene polymorphisms in healthy controls. Moreover, nicotine was shown to improve gating in subjects with both low baseline gating and COMT polymorphisms associated with reduced synaptic dopamine, and reduced gating in individuals with high baseline gating and COMT polymorphisms associated with higher synaptic dopamine (de la Salle et al, 2013). Dextroamphetamine reduced gating in healthy subjects (Light et al, 1999). The dopamine D2 receptor antagonist haloperidol also increases gating in individuals exhibiting low baseline gating and similarly disrupts gating in subjects with normal baseline gating (Csomor et al, 2008) and this same "inverted U" pattern of effect is observed with nicotine administration in the absence of other drugs (Knott et al, 2013).

A number of studies have found evidence that the modulation of serotonin and noradrenaline also affect P50 gating in healthy individuals. Mann et al (2008) observed a

disruption of P50 gating after simultaneously depleting serotonin and dopamine, but not after selective depletion of either serotonin or dopamine individually. Interestingly, selective reuptake inhibition of serotonin via 10mg escitalopram had no effect on gating (Jensen et al, 2007) while a dose of 15mg escitalopram significantly reduced gating (Oranje et al, 2010). Imipramine, which has anticholinergic properties at muscarinic receptors and which inhibits reuptake of serotonin, noradrenaline, and to a much lesser extent, dopamine, was found to decrease P50 suppression (Hammer et al, 2007). Ayahuasca, an herbal concoction which combines the psychedelic N,N-dimethyltryptamine (DMT) as well as MAO inhibiting agents, was shown to disrupt P50 gating in a dose-dependant manner (Riba et al, 2002). Increased noradrenergic transmission via yohimbine reduced gating, albeit in a small sample (Adler et al, 1994). In schizophrenia, selective antagonism of serotonin at the 5-HT_3 receptor improved P50 gating in medicated patients (Adler et al, 2005), and increased noradrenaline via clonidine normalized gating in schizophrenia except at a high dose (Oranje and Glenthøj, 2014). While few of these studies are directly comparable, overall it appears that P50 gating can be modulated differentially depending on the affected combination of monoamines, as well as the degree (dose) to which these monoamines are increased or decreased.

We hypothesized that inhibition of MAO-A via moclobemide would yield similar effects to the above described monoaminergic modulation in a sample of healthy individuals, i.e., the disruption of P50 gating in individuals with normal baseline gating and improvement of P50 gating in individuals with low baseline gating. Animal models have associated gating ability with the presence and function of hippocampal low affinity

nicotinic acetylcholine receptors (α7 nAChRs) (Luntz-Leybman et al, 1992; Stevens et al., 1996). In a computational model of hippocampal P50 gating, it was shown that dopamine may modulate the synchrony of gating response in nicotinic dependant GABAergic microcircuits in an inverted-U fashion, wherein optimal levels of dopamine yielded the most efficient gating and too much or too little dopamine resulted in disrupted gating via reduction in neuronal signal-to-noise ratio (Moxon et al, 2003). We thus further hypothesized that the combined nicotinic stimulation of inhibitory GABAergic interneurons and moclobemide-enhanced dopaminergic release would further improve P50 gating in healthy individuals exhibiting low baseline gating. In individuals with normal baseline gating, we hypothesized that this combination would rescue gating deficiencies seen with separate administration of moclobemide or nicotine, by returning hippocampal microcircuit signal-to-noise ratios to normal.

2.6. Materials and Methods

2.6.1. Subjects

This study was approved by and carried out in compliance with the Research Ethics Board of the Royal Ottawa Health Care Group as well as the University of Ottawa Research Ethics Board. Twenty-four healthy male volunteers were recruited by local advertisement. In order to avoid potential gender differences in gating (Hetrick et al, 1996), as well as possible menstrual cycle related variation in serotonin levels (Hindberg and Naesh, 1992), only male participants were included. All participants were non-

smokers, defined as having smoked less than 100 total lifetime cigarettes and none in the past year, as well as exhibiting expired carbon monoxide (CO) levels less than 3 parts per million. Prior to the first test session, participants underwent a medical evaluation as well as psychiatric interview using the structured clinical interview for DSM-IV-R Non-Patient Edition (SCID-NP) (First et al, 1995) and the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992). Volunteers were screened via self-report for current/past personal or family psychiatric (including alcohol/drug abuse/dependence), or neurologic (including seizures, head trauma with loss of consciousness < 1 hour within past 2 years) disorder, current use of medication (including over the counter medications and herbal medications), excessive caffeine use (> 4 cups of coffee/day or equivalent), body mass index (BMI) 20-30 kg/m², and audiometrically assessed normal hearing.

2.6.2. Experimental Design

Participants attended the laboratory on 4 test days (separated by a minimum of 48 hours) in a randomized, double-blind, placebo-controlled cross-over design, where counterbalanced drug combinations included Placebo/Placebo (PP), Moclobemide/Placebo (MP), Placebo/Nicotine (PNic), or Moclobemide/Nicotine (MNic).

2.6.3. Moclobemide Administration

75 mg Moclobemide (Manerix®, Hoffman-La Roche) was used to pharmacologically inhibit MAO-A. Moclobemide, having a mean Tmax of 49 minutes and elimination half life of 1.5 hours, decreases plasma 3,5-Dihydroxyphenylglycine (DHPG) by ~55% at 120 min (Hoffmann-La Roche, 2009). As such, this study used a single dose of 75 mg in order to achieve ~30-40% plasma DHPG reductions. To maintain a double-blind, the dose of moclobemide and the placebo (cellulose) were each placed in opaque capsules.

2.6.4. Nicotine Administration

Nicotine was administered in the form of two pieces (4mg + 2mg) of cinnamon-flavored Nicorette® gum (Johnson & Johnson Inc., Markham, Ontario, Canada). The total (6 mg) dose was used to achieve a similar blood nicotine level to that of an average smoker after smoking a single cigarette of average nicotine yield; i.e. 15-30 ng/ml (Hukkanen et al, 2005). Peak blood nicotine levels using this method and dose arise at approximately 30 min following the start of chewing. The elimination half-life of nicotine is ~120 min. Gum was chewed in accordance with manufacturer's guidelines, i.e. a chewing time of 25 minutes, biting twice every minute (as cued by audio recording) and "parking" gum between the teeth and cheeks between bites. Placebo gum was similar in size, color, texture, and taste. In addition, participants wore nose plugs throughout the chewing process in order to reduce any sensory differences between nicotine gum and placebo.

A physical-symptoms checklist (Harkrider and Hedrick, 2005) was used to measure the severity of nicotine related adverse symptoms as reported by each participant on each session. Symptoms (such as heart-pounding, headache, dizziness, and nausea) were

quantified on a 5-point scale where: 1 = “no symptoms”, 2 = “mild symptoms”, 3 = moderate symptoms”, 4 = “strong symptoms” and 5 = “extreme symptoms”.

2.6.5. Procedure

Prior to any testing session, participants were interviewed by the study psychiatrist to screen for any contraindications associated with the use of moclobemide. Participants attended four test sessions after 8 hours of abstinence from food, medicines, alcohol and caffeine. Upon arrival, CO levels were assessed in order to ensure CO levels below 3 ppm. Participants were then given a capsule containing either 75 mg moclobemide or placebo, after which they engaged in light reading during a 90 minute rest period in order to ensure TMax activity during recording. Electrodes were attached after this rest period, while the participant was given either nicotine or placebo gum. After hookup/gum chewing, the P50 paradigm was administered.

2.6.6. P50 ERP Acquisition

During the P50 paradigm, participants sat in a dimly-lit, sound attenuated chamber, and were instructed to keep their eyes open as they watched a silent nature movie, and to ignore the auditory stimuli presented binaurally through headphones. Sixty-four 85 dB (SPL) stimulus (“click”) pairs (S1-S2) were presented, all with 1ms stimulus durations and inter-stimulus intervals (between S1 & S2) of 500 ms and inter-pair intervals (between S2 & S1) of 10s. EEG was recorded from 8 scalp sites (F_Z, F_3, F_4, C_Z, C_3, C_4,

P_Z, O_Z) using a nose reference and a ground electrode positioned between FPz and Fz sites. Vertical (VEOG) and horizontal (HEOG) electro-oculographic activity was measured using additional electrodes above and below the right eye, as well as on the external canthus of both eyes, respectively. Electrode impedances were maintained below 5 kΩ and electrical activity was recorded using a Brain Vision V-8 Amplifier® (Brain Products, Germany) with bandpass filters set at 0.1-120Hz, digitized continuously at 500Hz by Brain Vision Recorder Software (Brain Products, Germany).

2.6.7. P50 ERP Processing

Offline analysis was performed using Brain Vision Analyzer® (Brain Products, Germany). Data was filtered (10Hz-50Hz) and segmented into 250 ms (50 ms pre-stim) epochs. Epochs were then corrected for eye movement and blink activity (Gratton et al, 1983), and artifacts (voltages exceeding ± 75 μV) were excluded from the analysis. When either an S1 or S2 segment was rejected, the corresponding, paired-segment (S1 or S2) was also excluded from analysis. Remaining epochs were baseline corrected (to 50 ms pre-stim), and averaged separately for S1 and S2.

Peak amplitudes for S1 and S2 were measured at the Cz site, with the stipulation that a P50 must be identifiable in at least one additional central site (i.e. C3/C4). Semi-automatic identification of P50 proceeded as described by Boutros et al. (2004). P50 was chosen as the second of two positive peaks, appearing as the largest positivity between 40 and 80 ms relative to pre-stimulus baseline, and following an earlier positive peak at 15-40 ms. The peak for S1 was used to guide the identification of the relative onset of S2. In

addition to peak amplitude and latency, both the ratio index (S2 P50 amplitude divided by S1 P50 amplitude) and difference score (S1 P50 amplitude minus S2 P50 amplitude) were derived as measures of sensory gating.

2.6.8. Statistical Analysis

Data was analyzed using IBM SPSS software. Amplitudes, latencies, and gating measures (rP50/dP50) were subjected to separate repeated measures analyses of variance (ANOVA) with drug and stimulus (S1/S2) as within-group factors. Significant effects and a priori hypotheses were followed up with pairwise comparisons. To test whether drug conditions differentially affected subjects with high (HG) or low (LG) baseline P50 gating as measured by the placebo (PP) condition, subjects were grouped via median-split into low (N = 12) and high (N = 12) gaters, as has been employed by previous studies (Csomor et al, 2008; Knott et al. 2010; de la Salle et al, 2013). In order to maintain consistency with the literature in using both rP50 and dP50 measures, separate repeated-measures ANOVAs were performed after grouping subjects by placebo rP50 (rHG vs. rLG) and after grouping subjects by placebo dP50 measures (dHG vs. dLG), with drug conditions as within-subject factors and gating group (HG vs. LG) as between-subject factors. Groups created using rP50 baselines differed from groups created using dP50 baselines by two participants. The Shapiro-Wilk test of normality was used for all datasets prior to analysis. Datasets that were not normally distributed were compared using the Wilcoxon signed-rank test; all other data were compared with paired-samples t-tests.

2.7. Results

2.7.1. Tests of Normality

For all subjects (N = 24) it was found that amplitude data for both S1 and S2 were not normally distributed, with the exception of S1 amplitude in the MP group. While dP50 scores were normally distributed, rP50 scores in the MP, PNic, and MNic conditions were not normally distributed. After segregating data into groups based on baseline rP50 scores, rLG amplitudes for S1 and S2 were not normally distributed with the exception of S1 amplitude in the MP group. rLG rP50 scores were not normally distributed in the PP and MP groups. rHG S1 amplitudes in the PP and MP groups, as well as rHG S2 amplitude in the MNic group were not normally distributed. rHG rP50 data was not normally distributed in the MNic group.

After segregating data into groups based on baseline dP50 scores, dLG S1 and S2 amplitudes were normally distributed while dHG S1 amplitudes were not normally distributed with the exception of the MP group, and dHG S2 amplitudes were not normally distributed in all groups. Both dLG and dHG dP50 scores were normally distributed.

Amplitudes, Latencies and Gating measures are summarized in Table 2.1.

Table 2.1: Mean amplitude (μV), latency (ms), and sensory gating characteristics (+ standard error) for overall (N=24) and subgroups stratified for low baseline (N=12) and high baseline (N=12 individuals) in placebo (PP), moclobemide, (MP), nicotine (PNic) and nicotine combined with moclobemide (MNic) sessions. Amplitudes and latencies are stratified based on rP50 gating scores. * ¥ ŧ ø † = significant difference in drug condition
‡ = significant difference where PNic > PP and PNic > MNic

	PP			MP			Pnic			Mnic		
	Overall	Low Group	High Group	Overall	Low Group	High Group	Overall	Low Group	High Group	Overall	Low Group	High Group
S1 Amplitude	4.722 (1.00)	5.283 (1.97)	4.161 (.48)	4.244 (.39)	4.316 (.60)	4.172 (.51)	4.686 (1.00)	5.972 (1.88)	3.400 (.59)	4.572 (.62)	5.307 (1.17)	3.836 (.35)
S2 Amplitude	2.727 (.82)	4.093 (1.54)	1.361 (.30)	2.103 (.34)	2.588 (.60)	1.617 (.27)	2.949 (.89)	3.846 (1.75)	2.052 (.31)	2.019 (.57)	2.995 (1.00)	1.044 (.45)
S1 Latency	61.83 (2.07)	59.667 (2.98)	64.000 (2.85)	61.917 (2.64)	62.667 (4.23)	61.167 (3.35)	60.417 (2.00)	58.500 (2.87)	62.333 (2.78)	61.500 (2.81)	60.667 (3.92)	62.333 (4.19)
S2 Latency	58.420 (1.96)	58.83 (3.19)	58.000 (2.41)	57.833 (1.99)	57.33 (2.59)	58.333 (3.12)	55.083 (1.67)	55.333 (2.90)	54.833 (1.81)	57.000 (2.73)	59.167 (4.19)	54.833 (3.57)
rP50	0.574* (.060	0.817¥ (.07)	0.331‡ (.05)	0.617 (.12)	0.743 (.21)	0.491 (.09)	0.684ŧ (.10)	0.635 (.14)	0.734‡ (.14)	0.405*ŧ (.08)	0.537¥ (.07)	0.274‡ (.13)
dP50	1.995 (.34)	0.775ø (.20)	3.214† (.42)	2.141 (.46)	1.919 (.60)	2.364 (.71)	1.737 (.43)	1.830 (.69)	1.644† (.53)	2.552 (.33)	2.144ø (.52)	2.960 (.41)

2.7.2. P50 Amplitudes

Grand averaged waveforms for S1 vs. S2 in each drug condition are shown in Figure 2.1. Analysis of P50 Amplitudes resulted in a significant main effect of stimulus, $F(1,23) = 61.275$ $p < .000$, due to larger overall amplitudes of S1 (M = 4.556 μV, SE = .67) compared to S2 (M = 2.450 μV, SE = .63), $t(23) = 7.83$. There was no significant stimulus by drug interaction. Follow up comparisons confirmed there were no significant differences between drug conditions for either S1 or S2 amplitudes.

After segregation of low and high baseline gating based on rP50, no significant stimulus x group, drug x group, or stimulus x group x drug interactions were observed. However, planned comparisons revealed larger rLG S2 amplitudes in the PP condition (M = 4.093, SE = 1.54) compared to the MNic condition (M = 2.995, SE = 1.00) $Z = 1.96$, $p = 0.05$. Segregating groups based on dP50 revealed a significant drug x stimulus x group interaction $F(3,66) = 3.143$, $p = 0.045$, due to larger dHG S1 amplitudes in the PP condition (M = 6.359 μV, SE = 1.88) compared to both the PNic condition (M = 5.160 μV, SE = 1.92) $Z = -2.35$, $p = 0.019$. The low gating group showed lower dLG S1 amplitudes in the PP condition (M = 3.085 μV, SE = .35) compared to the MP condition (M = 4.038 μV, SE = .52) $t(11) = 2.285$, $p = 0.043$, as well as compared to the PNic condition (M = 4.212 μV, SE = 1.44) $t(11) = 2.084$, $p = 0.061$ and to the MNic condition (M = 4.134 μV, SE = .49) $t(11) = 3.106$, $p = 0.010$.

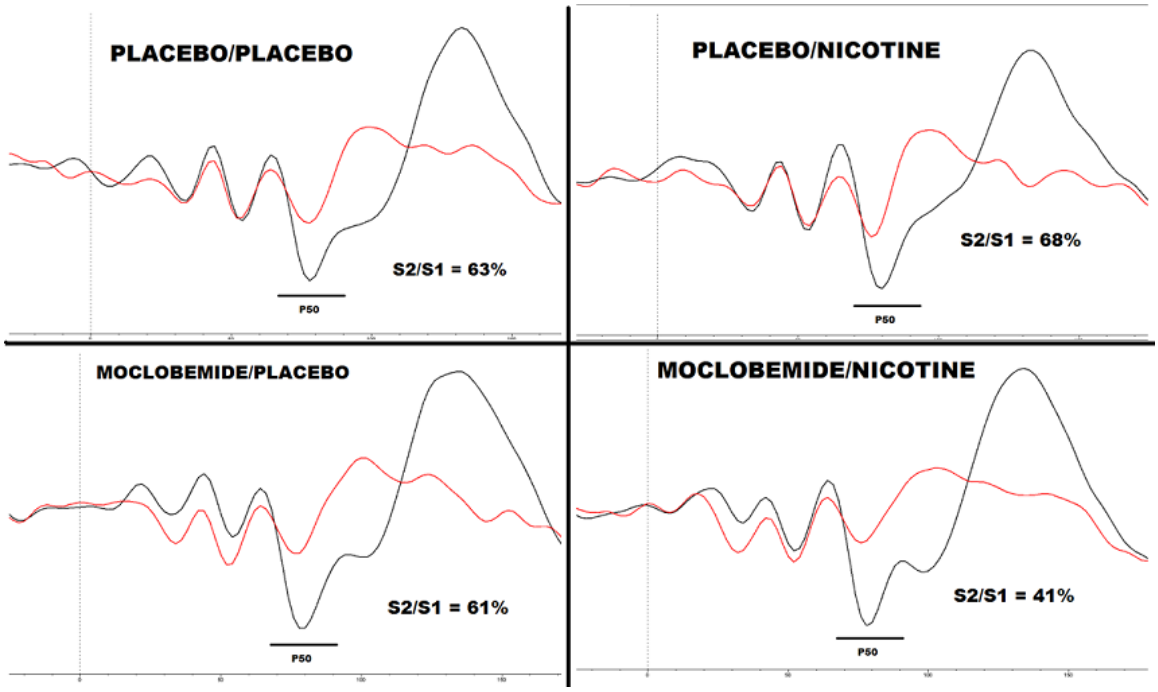

Figure 2.1: Grand averaged (N =24) waveforms and amplitude suppression ratio scores for each treatment (PP, MP, PNic, and MNic) condition. Average S1 shown in black (dark) and average S2 shown in red (light).

2.7.3. P50 Latencies

Analysis of P50 latencies showed a significant main effect of stimulus, $F(1,23) = 6.080$, $p = 0.022$ due to longer overall latencies for S1 (M = 61.417 ms, SE = 2.01) compared to S2 (M = 57.083 ms, SE = 1.45), $t(23) = 2.47$. Pairwise comparisons revealed that only the PNic condition yielded significant differences in latency between S1 (M = 60.417 ms, SE = 1.99) and S2 (M = 55.083 ms, SE = 1.67) $t(23) = 2.43$. There was no significant stimulus by drug interaction. Follow up analysis confirmed there were no significant differences between drug conditions for either S1 or S2 latencies.

After segregation of low and high baseline rP50 gating, no significant stimulus x group, drug x group, or stimulus x group x drug interactions were observed. Segregating groups

based on dP50 revealed a significant stimulus x group interaction, F(1,22) = 5.738, p = 0.026 due to longer dHG S1 latencies (M = 62.917 ms, SE = 2.87) compared to S2 latencies (M = 54.750 ms, SE = 1.97) t(11) = 3.61 p = 0.002.

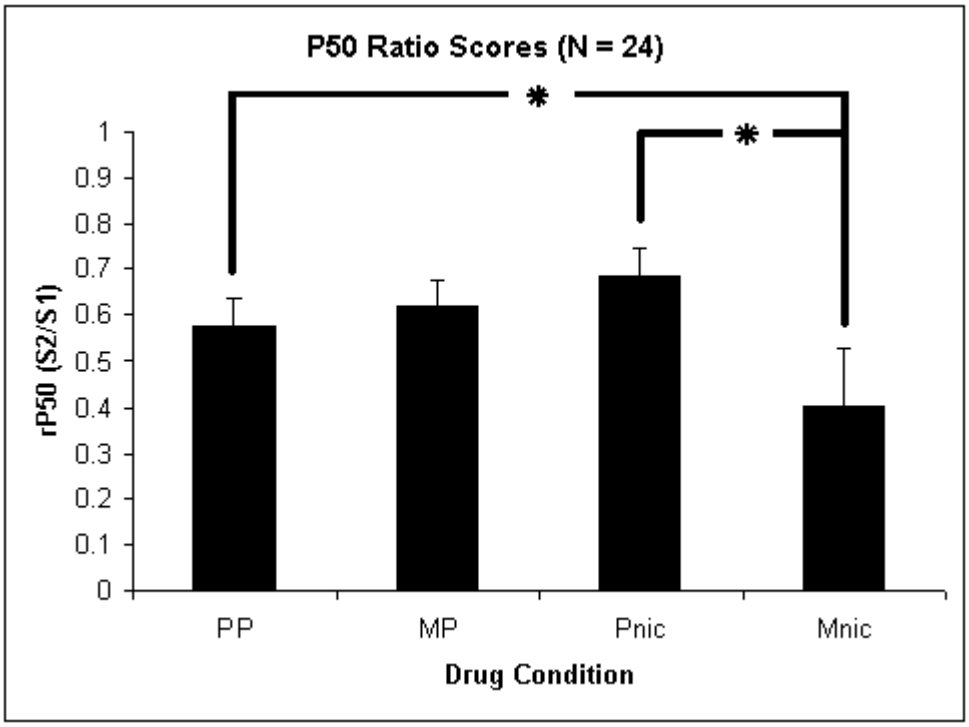

Figure 2.2: rP50 scores (higher score = decreased gating) for each treatment condition for all (N=24) participants. PP = Placebo, MP = Moclobemide , PNic = Nicotine, and MNic Moclobemide+Nicotine.

2.7.4. P50 Gating Measures

Overall analysis of rP50 and dP50 gating measures yielded no significant main effects. Planned comparisons revealed significantly lower rP50 scores in the MNic session (M = 0.405, SE = .08) compared to the PP session (M = 0.574, SE = .06) Z = 2.34, p = 0.019 (Figure 2.2). The MNic group also exhibited significantly lower rP50 scores compared to the PNic session (M = 0.684, SE = .10) Z = 2.00, p = 0.046.

After grouping participants based on low and high baseline rP50 gating, no significant drug x group interactions were found. Planned comparisons revealed a significant difference between rLG rP50 scores in the PP condition (M = 0.817, SE = .07) and rLG rP50 scores in the MNic condition (M = .537, SE = .07) Z = 2.35, p = 0.019, as well as significantly reduced rHG rP50 gating in the PNic condition (M = 0.734, SE = .14) compared to both the PP condition (M = 0.331, SE = .05) t(11) = 2.99, p = 0.012 and the MNic condition (M = 0.274, SE = .13) Z = 2.43, p = 0.006 (Figure 2.3).

After grouping participants based on low and high baseline dP50 gating, there was a significant group x drug interaction F(1,22) = 3.143, p = 0.045 due to significantly lower dLG dP50 scores in the PP condition (M = 0.775 μV, SE = .20) compared to the MNic condition (M = 2.144 μV, SE = .52) t(11) = 2.73, p = 0.020, as well as significantly reduced dHG dP50 scores in the PNic condition (M = 1.644 μV, SE = .53) compared to the PP condition (M = 3.214 μV, SE = .42) t(11) = 2.79, p = 0.018.

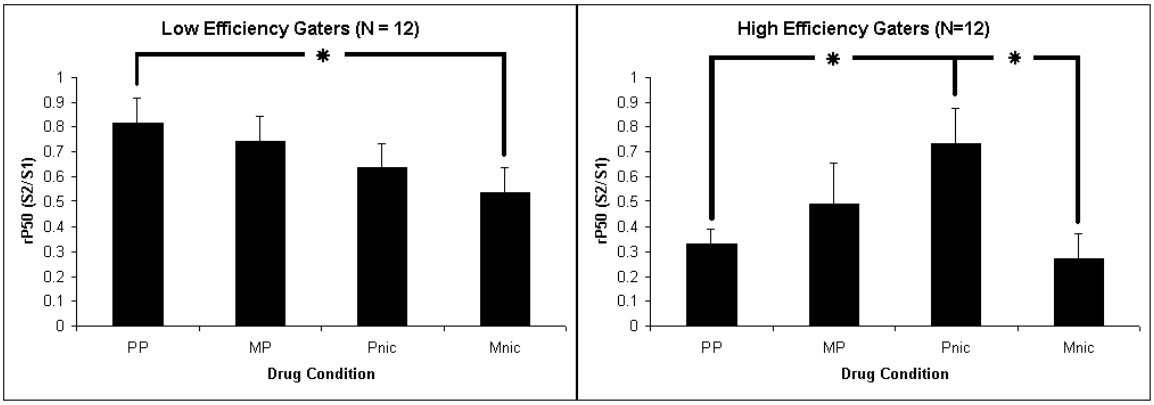

Figure 2.3: Left: rP50 scores in each treatment condition for participants stratified for low baseline gating (N=12). Right: rP50 scores in each treatment session for participants stratified for high baseline gating (N=12). PP = Placebo, MP = Moclobemide , PNic = Nicotine, and MNic Moclobemide+Nicotine.

2.7.5. Adverse Events

There was a significant effect of drug $F(1,23) = 1.643$, $p = 0.033$ due to higher severity ratings for symptoms in the PNic session (M = 1.33, SE = .00), compared to the PP session (M = 1.00, SE = .00) $t(23) = 0.23$, $p = .029$ as well as compared to the MNic session (M = 1.00, SE = .00) $t(23) = 0.23$, $p = .029$.

2.8. Discussion

The present study was designed to investigate the separate and combined effects of acute nicotine administration and MAO-A inhibition via moclobemide on gating of the P50 auditory event related potential. Though there was no main effect overall, planned comparisons revealed significantly reduced rP50 gating ratios after the combination of moclobemide and nicotine compared to placebo and to nicotine alone. Importantly, while nicotine generally improves rP50-measured gating in low baseline gating individuals (Knott et al, 2013), improvement by nicotine in our low baseline gating sample did not reach significance. The combination of moclobemide and nicotine did significantly improve gating in low baseline gating individuals, suggesting that the interaction of nicotine and monoamine oxidase A inhibition yields a more robust effect on the neural systems underlying gating than does nicotine alone.

Moreover, our high baseline gating sample exhibited results similar to those seen in previous studies (Knott et al, 2010; 2013) with nicotine significantly attenuating gating in these individuals. Interestingly, the combination of moclobemide and nicotine did not attenuate gating in the high baseline gating group; participants in this condition exhibited gating measures similar to baseline. It seems possible that the previously observed

"inverted U" relationship between cognitive function and nicotine (Newhouse et al, 2004), with nicotine ameliorating cognition in low functioning individuals but inhibiting performance in optimally performing individuals, may be overridden by enhanced monoamine availability achieved through MAO-A inhibition, though whether this effect extends beyond P50 gating remains to be seen.

While dP50 did not show a significant overall (un-segregated) effect, the general direction across drug conditions was similar to our rP50 results, with the lack of dP50 significance possibly due to this measures' higher sensitivity to S1P50 amplitude (Fuerst et al, 2007; Lu et al, 2007). This same phenomenon might also have contributed to our finding no interaction between drug, baseline group, and amplitude using rP50 baseline segregation, compared to dP50 segregation where the interaction was significant, and larger baseline S1P50 amplitudes were observed in the high gating group compared to the nicotine and moclobemide condition. However, the finding that rP50 segregation elucidated larger placebo S2P50 amplitudes in the low gating group compared to the nicotine and moclobemide condition suggests that these results are not simply a consequence of S1P50 modulation alone. This supports the interpretation that these are indeed sensory gating effects, as opposed to a modulation of S1-dependant sensory registration. The differences in S1P50 vs. S2P50 latencies were also specific to dP50 segregation and were significant only in the high baseline gating group; a finding not reported in previous studies and which may be specific to our sample.

Moclobemide in the absence of nicotine did not affect gating overall or after segregation compared to both placebo or to the moclobemide-with-nicotine condition. However, the direction of our results suggests that moclobemide-induced monoamine oxidase

inhibition trended in a direction similar to nicotine's effects, in that mean gating values were improved, albeit non-significantly, compared to baseline in the low baseline group and diminished in the high baseline group. It is possible that either a higher dose or a larger sample size may have yielded significant differences between moclobemide and placebo gating scores, similar to previous studies that have shown baseline-dependant differences following monaminergic modulation via haloperidol (Csomor et al, 2007) and sertindole (Holstein et al, 2011).

Inconsistent with previous studies, nicotine in the absence of moclobemide did not significantly improve gating in the low-baseline group. Although similar to moclobemide, mean ratios trended in a direction of improvement compared to placebo. It is possible that this trend did not reach significance due to the fact that no "mid range" gating group was stratified in the current study due to a smaller sample size than was used in Knott et al, (2013), which would eliminate the possibility of relatively high gating individuals being stratified into the low group after median-split. Another possibility is the gene-specific differential effects of nicotine observed by de la Salle et al, (2013), in that nicotine's improvement in low baseline suppressors is more evident in carriers of the homozygous valine (Val/Val) variant of the COMT polymorphism compared to that of homozygous methionine (Met/Met) variant carriers. A disproportionate number of Met/Met allele carriers in the current low group could have prevented nicotine-driven improvements from reaching significance. Future studies may benefit from grouping subject based on genotype in addition to baseline gating.

As in Moxon et al (2003)'s simulation, the most robust improvement of gating in this experiment occurred with the simultaneous promotion of monoaminergic release and

nicotinic activation. Our results support findings where atypical antipsychotic drugs differentially improve gating depending on their ability to target multiple neurotransmitter systems (e.g. cholinergic, serotonergic, dopaminergic) simultaneously (Adler et al, 2004). In healthy individuals, it has been shown that normal gating is only diminished following the simultaneous depletion of dopamine and serotonin, but not when either monoamine is depleted individually (Mann et al, 2007). Thus it would seem that optimal availability of dopamine and serotonin are necessary for efficient gating, and that cholinergic activation contributes to the normalization of this availability, as was seen in our high baseline gating group in the MNic condition.

This study is limited to event related potential data and as such we can only assume that the monoamine modulating properties of moclobemide are responsible for the reported effects. Although subjects were asked to abstain from food prior to each test session, we did not control for day-to-day consumption of dietary choline or for foods with monoamine oxidase inhibitory properties. Although subjects reported greater adverse symptoms during the PNic condition compared to the PP and MNic condition, mean symptoms were very low, with the PNic group exhibiting a mean score of 1.33 where a score of 1 indicates no adverse symptoms at all. Thus it is not likely that physical symptoms contributed to ERP results, though they cannot be ruled out entirely.

Care should be taken when interpreting the high vs. low baseline (placebo) comparisons in this study, as the use of the median split has been shown to decrease effect size and may produce misleading results (MacCallum et al. 2002); though we deemed this method appropriate for the current study due to the previously observed differential effects of nicotine in high vs. low gating individuals (Knott et al. 2010), as well as the importance

of utilizing our low gating group to serve as a model of gating deficits in schizophrenia. In our low group, mean ratio scores were 0.82, comparable to Patternson et al (2008)'s meta-analysis which found mean schizophrenia ratio scores to be 0.80. Although we did control for family history of psychosis in our healthy control sample, we cannot determine if deficient gating in our low-gating group was due to common mechanisms. One possibility is that our low-gaters share common nicotinic receptor polymorphisms (Houy et al. 2004), however we lack the genetic data necessary to confirm this hypothesis. Finally, due to the relatively low number of electrodes (8 scalp sites), we cannot reliably report differences in brain region activation. Follow-up experiments are necessary to investigate the effects of MAO-B inhibition as well as combined MAO-A and MAO-B inhibition on gating with and without nicotine. A sample of non-smoking schizophrenia patients will also be necessary to confirm whether the gating improvements in our low-gating group translate to the patient population, though the effects of treatment/medication would have to be taken into account.

2.9. Conclusion

This study supports the hypothesis that the ratio index of P50-measured sensory gating can be improved under conditions of acute nicotine and MAO-A inhibition in healthy individuals, and specifically, in individuals with low baseline gating. The improvement in P50 ratio in the current sample seems to be a result of true gating and not simply auditory registration. As this effect was seen in individuals with low baseline gating, a group that has been used as a healthy control model of schizophrenia (Light and Braff, 2003;

Csomor et al, 2008), the current study provides corroborating evidence that the theorized self-medicating smoking behavior of neuropsychologically impaired populations (e.g. schizophrenia) is not solely driven by activation of nicotinic receptors, and instead may be due to a more complex MAO/nicotine interaction. Furthermore, MAO inhibition eliminates the detrimental effects of nicotine on high-baseline gating individuals. Future studies on smoking and cognition should take into account the neuromodulating properties of non-nicotinic agents in tobacco in order to more accurately model smoking in laboratory paradigms. Clinicians may benefit from considering the smoking status of patients when determining treatment, particularly for heavy smokers who may exhibit robust MAO inhibition, due to the potential interaction of smoking with monoaminergic or cholinergic based medication.

2.10 Funding and Disclosure

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CHAPTER 3

The separate and combined effects of monoamine oxidase inhibition and nicotine on the mismatch negativity event-related potential

3.1 Overview

This manuscript provides an investigation into the separate and combines effects of nicotine and moclobemide on the MMN ERP paradigm. The previous chapter focused on P50 gating, which has been strongly associated with cholinergic abnormalities in SZ. The MMN is also strongly associated with SZ, but has been more closely related to NMDAR dysfunction. Because of the synergistic effects of nicotine and moclobemide on P50 gating, an investigation of these same drug effects on MMN may elucidate the specificity of the nicotine/MAO-inhibition interaction on these two auditory ERP paradigms. If these two auditory ERPs are indeed modulated by different neural mechanisms, we expect a different effect of each drug condition on these two paradigms; while there is some evidence that nAChRs can modulate MMN, there is no evidence that monoaminergic modulation plays a role. In this study, participants are also stratified based on MMN amplitude in order to elucidate any inverted-U effects of each drug condition.

3.2 Statement of author contribution

The initial experimental design of this study was drafted by Verner Knott and Pierre Blier, with input by Dylan Smith. Participants were recruited, screened and given orientations by Dylan Smith, with psychological and pharmacological screenings also performed by Vadim Ilivitsky. Programming of experimental stimuli was completed by Derek Fisher and Dylan Smith. ERP recording/analysis, statistical analysis, writing of the manuscript and generation of figures was completed by Dylan Smith. All authors critically reviewed and approved the final manuscript. This study was supported by a University of Ottawa Medical Research Fund grant awarded to Verner Knott.

3.3. Title page

The Separate and Combined Effects of Monoamine Oxidase A Inhibition and Nicotine on the Mismatch Negativity Event Related Potential

Dylan M Smith[1,2] B.Sc, Derek Fisher[3] Ph.D, Pierre Blier[1,2,4]MD, Vadim Illivitsky[4] MD, Verner Knott[1,2,4] Ph.D.

[1] University of Ottawa Institute of Mental Health Research, Ottawa, Ontario, Canada
[2] Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada
[3] Department of Psychology, Mount Saint Vincent University, Halifax, Nova Scotia, Canada
[4] Royal Ottawa Mental Health Centre, Ottawa, Ontario, Canada

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3.4. Abstract

The Mismatch Negativity (MMN) auditory event-related potential (ERP) has been extensively studied as a potential biomarker for abnormal auditory processing in schizophrenia (SZ), a population which exhibits abnormally high smoking rates. The relationship between nicotinic activation and cognition in SZ may be related to underlying nicotinic and NMDA receptor dysfunction within the disease. However, transient cognitive improvements via smoking in patients may also result from monoamine oxidase (MAO) inhibition, achieved through tobacco smoke. In 24 healthy non-smoking males, we investigated the separate and combined effects of nicotine and MAO-A inhibition via moclobemide (75 mg) on the optimal-5 variation of the MMN paradigm. No significant drug effects were observed in our total sample, however, stratification of individuals into Low (N = 12) and High (N = 12) baseline MMN amplitude groups revealed increases in duration MMN amplitude relative to placebo by nicotine, as well as moclobemide, but not after the combination of the two. Because previous research has shown no effect of monoamine modulation on MMN, this study shows an unexpected effect on MMN via moclobemide.

Keywords: Nicotine, MAO inhibition, mismatch negativity, moclobemide, schizophrenia

Abbreviations: MMN, Mismatch Negativity; ERP, event-related potential; SZ, schizophrenia; MAO, monoamine oxidase; nicotinic acetylcholine receptor, nAChR; GABA, γ-Aminobutyric acid; NMDAR, N-methyl-D-aspartate receptor; PCP, phencyclidine; 5-HT, serotonin; D1, Dopamine Receptor 1; D2, dopamine receptor 2;

ATD, acute tryptophan depletion; BMI, body mass index; SSRI, selective serotonin reuptake inhibitor; DSM, diagnostic and statistical manual of mental disorders; SCID-NP, structured clinical interview for DSM-IV-R Non-Patient Edition; FIGS, family interview for genetics studies; PP, placebo/placebo; MP, moclobemie/placebo; PNic, placebo/nicotine; MNic, moclobemide/nicotine; DHPG, 2,5-dihydroxyphenylglycine; CO, carbon monoxide; VEOG, vertical electrooculogram; HEOG, horizontal electrooculogram;

3.5. Introduction

The high prevalence of tobacco smoking behavior among schizophrenia (SZ) patients (Lawrence et al, 2009) has been proposed to result from patients' need to counteract core cognitive deficits associated with nicotinic acetylcholine receptor (nAChR) dysfunction in SZ (Kumari and Postma, 2005). While a number of studies have investigated nicotine's effect on cognitive processing in SZ (Evans and Drobes, 2009; Gehricke et al, 2007; Kumari and Postma, 2005; Leonard et al, 2007; Ochoa and Lasalde-Dominicci, 2007; Wing et al., 2012; Winterer, 2010), including deficits in the auditory mismatch negativity (MMN) event-related potential (ERP) (Javitt, 1995; Inami et al, 2007), it is not known if the monoamine oxidase (MAO) inhibiting agents in tobacco smoke (Herraiz and Chaparro, 2005) also affect early auditory cognitive processing such as that indexed by the MMN.

SZ is associated with a number of behavioral abnormalities, including positive (e.g. hallucinations, delusions) and negative (e.g. flattened affect, anhedonia) symptoms, as well as deficits of cognition thought to be core to the disorder (Elvevag et al, 2000).

Cognitive deficits arise prior to psychosis (Caspi et al, 2003), are largely resistant to medications (Hill et al, 2010), and are associated with functional outcome (Green et al, 2000). These findings have led to a focus on cognition-improving strategies for SZ patients, including the NIMH-MATRICS initiative (Marder, 2006), in hopes of developing treatments which promote functional outcome and recovery.

While smoking is strongly associated with addiction and addiction-related effects (Jasinka, 2013), there is evidence that nicotine has pro-cognitive effects in certain domains, including working memory and executive functioning (Swam and Lessov-Schlaggar, 2007). These have been theorized to result from nicotine's actions on nicotinic acetylcholine receptors, and specifically, the α7 nAChR located on GABAergic interneurons of key structures, such as the prefrontal cortex, hippocampus, thalamus and ventral tegmental area (Mansvelder et al, 2006).

Nicotine's effects at the α7 nAChR may be particularly important in SZ, where there is evidence of receptor dysfunction in patients (Young and Geyer, 2013). The locus containing CHRNA7, the gene which encodes the α7 nAChR, has been linked to high risk for schizophrenia in genome-wide association studies (Stefansson et al, 2008). This gene has also been associated with deficient P50 suppression, an ERP-indexed measure of auditory sensory gating known to be abnormal in SZ (Freedman et al, 1997). Post-mortem studies have found reductions in α7 nAChR protein binding in prefrontal cortex (Martin-Ruiz et al., 2003) cingulate cortex (Marutle et al, 2001) thalamic reticular nucleus (Court et al., 1999), and hippocampus (Freedman et al, 1995). The relatively low sensitivity to nicotine exhibited by the α7 nAChR (compared to the higher sensitivity α4β2 receptor) might explain the unique smoking behavior of SZ patients, who have been

shown to extract more nicotine per cigarette on average than non-SZ smokers (Olincy et al, 1997).

Recently, primate studies have shown α7 nAChR stimulation to be essential for normal functioning of glutametergic N-methyl-D-aspartate receptor (NMDAR) mediated working memory circuits in the dorsolateral prefrontal cortex (Yang et al, 2013). Subchronic administration of phencyclidine (PCP), an NMDAR antagonist, reduced binding of a selective nAChR radioligand ([^{11}C]CHIBA-1001) in the frontal cortex of rhesus monkeys (Hashimoto et al, 2012). In SZ, NMDA receptor hypofunction has been proposed as central to the pathophysiology of the disease (Javitt, et al, 2012). NMDAR antagonists, such as ketamine, mimic symptoms of SZ in healthy volunteers, including positive, negative, and cognitive symptoms (Lahti et al, 2001). Modern pathophysiological models of SZ include NMDA dysfunction in neural structures such as the hippocampus (Lodge and Grace, 2011) and thalamus (Clinton and Meador-Woodruff, 2004) with dopamine irregularities arising as a downstream effect.

Importantly, the effect of smoking on the modulation of dopamine and other monoamines is not a purely nicotinic phenomenon. It has been established that chronic smoking can inhibit both isoforms of MAO; MAO-A by ~28% (Fowler et al, 1996[a]) and MAO-B by ~40% (Fowler et al, 1996[b]) through the actions of β-carboline alkaloids in tobacco smoke (Herraiz and Chaparro, 2005). MAO-A may be of particular importance to the cognitive effects of chronic smoking due to its selectivity for oxidation of serotonin and noradrenaline, as well as its oxidative actions on dopamine, which it shares with MAO-B as a non-selective substrate (Finberg, 2014). It was previously shown that selective pharmacological inhibition of MAO-A, when combined with acute nicotine via chewing

gum, improves P50 sensory gating in healthy, non-smoking males (Smith, 2014) and these effects are more pronounced in individuals with low baseline gating. However, it is not known whether this effect extends to other sensory and cognitive processes, such as MMN-indexed sensory memory.

MMN, in its basic form, is an index of auditory change detection, typically measured as a scalp-recorded auditory ERP proceeding a “deviant” tone within a train of standard tones, (Näätänen et al, 2007) and is thought to represent sensory memory encoding in the brain. The “optimal" MMN paradigm (Näätänen et al, 2004) involves a series of short standard tone “pips” interspersed with 5 types of deviant tones comprised of variants (in relation to the standard) in duration, frequency (pitch), intensity (loudness), aural location, as well as a “gap” deviant created by eliminating sound from the middle portion of the standard tone. MMN, and particularly the duration deviant, has been well documented as deficient in SZ (see Näätänen et al, 2009 for review) and this deficit has been hypothesized to result in part from NMDAR dysfunction due to observations that NMDA antagonists block MMN generation in primates without affecting primary auditory processing (Javitt et al, 1996). Interestingly, duration MMN specifically has been shown to predict conversion to psychosis in at-risk individuals (Näätänen et al, 2015), supporting laboratory modulation of MMN as a useful model for preliminary research into the cognitive deficits underlying SZ.

The effects of nicotine on MMN have been investigated in a number of studies. Nicotine improved MMN in smokers by increasing amplitude to the standard tone in a roving paradigm utilizing continuously changing stimuli (Baldeweg et al, 2006), and improved MMN to an interstimulus interval deviant in both smokers and non-smokers

(Martin et al, 2009). In a consonant-vowel variation of the MMN paradigm, nicotine increased MMN amplitudes in smokers and non-smokers (Harkrider and Hedrick, 2005). Nicotine delivered via patch shortened latencies to a frequency deviant but did not affect amplitude (Inami et al, 2005). A selective agonist of the α4β2 nAChR increased amplitude and reduced latency to frequency deviants in non-smokers (Dunbar et al, 2007). Overall, it seems nicotine in the absence of monoaminergic modulation can affect MMN, however, because of varying methods and heterogeneous samples, often combining smokers and non-smokers, few of the studies to date are directly comparable, and no attempts have yet been made to separately elucidate the effects of nicotine and MAO inhibition on MMN.

The effect of MAO inhibition on MMN is not known, however, modulation of MAO-A substrates such as dopamine, serotonin, and norepinephrine and their effects on MMN have been studied using a variety of methods in healthy individuals. Haloperidol, a dopamine D2 receptor antagonist, increased MMN amplitudes to frequency deviants (Kähkönen et al, 2001), but failed to alter MMN in later studies (Kähkönen et al, 2002) with one study finding no effect of haloperidol on either frequency or duration MMN (Pekkonen 2002). Dopamine receptor activation via D_1 agonist bromocriptine, and D_1/D_2 agonist pergolide (Leung et al, 2007) both had no effect on duration MMN. Methylphenidate, a dopamine and norepinephrine reuptake inhibitor, had no effect on MMN frequency or duration (Korostenskaja, 2008). Acute tryptophan depletion (ATD), a method of decreasing serotonin synthesis, has increased MMN amplitudes to duration and frequency deviants (Kähkönon et al, 2005), however, a more recent study found no effect of ATD on MMN (Leung et al, 2010). Escitalopram, a selective serotonin reuptake

inhibitor (SSRI) increased amplitude to frequency MMN at moderate (Oranje et al, 2008) and high doses (Wienberg, 2009). 5-HT_{2A} receptor activation via psilocybin had no effect on frequency or duration MMN (Umbricht et al, 2002; 2003). Norepinephrine increase via atipamezole, an $alpha_2$ receptor antagonist also had no effect on MMN (Mervaala et al 1993) nor did growth hormone response measurements to apomorphine and clonidine neuroendocrine challenge tests, measurements of dopamine and norepinephrine system activation, respectively (Hansenne et al, 2003).

The objective of the present study was to determine the separate and combined effects of nicotine and MAO-A inhibition on MMN, while avoiding confounding effects of clinical and/or smoking status. Taken together, previous studies seem to suggest that nicotine can affect MMN while modulation of MAO-A substrates does not. Therefore, we hypothesized that pharmacological inhibition of MAO-A would not affect nicotine's ability to improve MMN in a group of healthy non-smokers. It has previously been observed that nicotine fails to alter frequency MMN in a group of smokers (Knott et al, 2006) who would presumably also be under the effects of MAO inhibition due to smoking status. However, nicotine has been shown to increase duration MMN amplitude in a group of smoking SZ patients (Dulude et al, 2009). Thus it is possible that nicotine's effects on MMN depend on both smoking as well as clinical status, and that these differences may differentially affect each type of deviant. Furthermore, because the effect of nicotine on MMN has been shown to be baseline and deviant dependant in healthy non-smokers (Knott et al, 2014a) with the response of low-baseline individuals mimicking what is seen in SZ, we further hypothesized that MAO-A inhibition would block alterations of MMN by nicotine in individuals with high baseline MMN, as in non-

clinical smokers, and MAO-A inhibition would fail to prevent improvement of MMN by nicotine in individuals with low baseline MMN, in particular duration deviant, as in schizophrenia.

3.6. Methods

3.6.1. Study participants

This study was approved by and carried out in compliance with the Research Ethics Board of the Royal Ottawa Health Care Group as well as the University of Ottawa Research Ethics Board. Twenty-four healthy right-handed males were recruited by local advertisement and screened for current, past, or family (1^{st} degree relative) psychiatric (including substance dependence) and neurologic disorder and/or trauma, medication use (including over-the-counter medication / herbal medication), excessive caffeine use (cut off: > 4 cups/day or equivalent), and body mass index (BMI) 20-30 kg/m^2. Only males were selected in order to avoid potential confounding effects of menstrual cycle variation in serotonin levels (Hindberg and Naesh, 1992). All participants were non-smokers, defined as having smoked less than 100 total lifetime cigarettes and zero cigarettes in the past year, as well exhibiting expired carbon monoxide (CO) levels less than 3ppm. All participants were evaluated as eligible for participation via screening interview using the structured clinical interview for DSM-IV-R Non-Patient Edition (SCID-NP) (First et al, 1995) and the Family Interview for Genetic Studies (FIGS) (Maxwell 1992), as well as an audiometric assessment for normal hearing.

3.6.2. Experimental design

Participants attended one orientation (non-experimental) session in the lab to familiarize themselves with procedures and equipment. On four separate experiment days, separated by minimum 48 hours, in a randomized, double-blind, placebo-controlled crossover design, participants were administered drug combinations including placebo/placebo (PP), moclobemide/placebo (MP), placebo/nicotine(PNic), or moclobemide/nicotine (MNic).

3.6.3. Moclobemide administration

Prior to participation, participants were interviewed by the study psychiatrist to screen for any contraindications associated with the use of moclobemide. 75 mg moclobemide (Manerix®, Hoffman-La Roche) was used to pharmacologically inhibit MAO-A, with a Tmax of 49 minutes and 1.5 hour elimination half-life, shown to decrease plasma 2,5-dihydroxyphenylglycine (DHPG), a measurement of MAO activity, by ~55% at 120 min (Hoffman-La Roche Ltd 2009). This dose was used to attain ~30-40% plasma DHPG reductions in order to model inhibition observed in chronic smokers (Fowler et al, 1996[a]). Both moclobemide and placebo (cellulose) were placed in opaque capsules.

3.6.4. Nicotine administration

In order to achieve similar blood-nicotine levels to that of an average smoker after a single cigarette of average nicotine yield, i.e., 15-30 ng/ml (Hukkanen et al, 2005), 6 mg cinnamon-flavoured Nicorette® gum (Johnson & Johnson Inc., Markham, Ontario, Canada) was administered via 2 pieces (4 mg + 2 mg) and chewed in accordance with manufacturer's guidelines, i.e., a chewing time of 25 minutes, biting twice every minute (as cued by audio recording), and "parking" gum between the teeth and cheeks between bites. This method and dose yields peak blood nicotine levels at approximately 30 minutes following the start of chewing with an elimination half-life of ~120 minutes (Le Houezec, 2003). Two pieces of placebo gum was used, similar in size, colour, texture, and taste. Participants wore a nose-plug while chewing in order to further reduce and perceivable differences between nicotine gum and placebo.

On each session, severity of nicotine related symptoms were measured using a checklist (Harkrider and Hedrick, 2005) as reported by the participant. Symptoms such as heart pounding, headache, dizziness, and nausea were quantified on a five-point scale where 1 = no symptoms, 2 = mild symptoms, 3 = moderate symptoms, 4 = strong symptoms, and 5 = extreme symptoms.

3.6.5. Experimental procedure

Test sessions were conducted between 9:00 am and 1:00 pm after 8 hours of abstinence from food, medicines, alcohol, and caffeine, with all four sessions starting at the same time of day for each participant. Carbon monoxide (CO) levels were measured upon arrival at the start of each session to ensure non-smoking compliance as screened by a

cut-off of 3 ppm. Participants were orally administered a capsule containing either 75 mg moclobemide or placebo, after which they were seated and engaged in light reading during a 90 minute rest period to ensure Tmax activity during recording. Electrodes were attached at the end of this rest period, while the participant chewed either nicotine or placebo gum. After the hookup and chewing session, the MMN paradigm was administered.

3.6.6. MMN paradigm

During recording of the MMN, participants watched a silent, neutral content video (The Blue Planet, BBC 2001). The optimal MMN paradigm (Näätänen et al. 2004) was comprised of 70 dB auditory tones delivered binaurally through headphones, and consisted of standard (p = 0.5) stimuli composed of 500, 1000, and 1500 Hz pure tones of 75 ms duration that were randomly intermixed with deviant (p = 0.5) stimuli. Stimulus onset asynchrony was constant at 500 ms. Duration deviants were 25 ms in length. Half of the frequency deviants were 10% lower in pitch (composed of 450, 900, and 1350 Hz partials) and half were 10% higher (composed of 550, 1100, and 1650 Hz partials). Half of the intensity deviants were 10 dB louder (80 dB) and half were 10 dB lower (60 dB). Location deviants were simulated by an 800 μs time difference between channels (half were delayed in the right channel and half were delayed in the left channel), creating a perceived change in location of approximately 90º. Gap deviants were created by removing 7 ms (with 1ms rise and fall) from the middle of the standard tone. In total, 5535 stimuli were presented across three blocks, lasting a total time of 15 minutes. Each

block began with 15 standards followed by a sequence in which every second tone was a deviant, with one deviant of each type presented once every five deviants, and with the restriction that deviants of the same category were never presented consecutively.

3.6.7. ERP recording

ERPs were recorded from 8 scalp sites (F_Z, F_3, F_4, C_Z, C_3, C_4, P_Z, O_Z) via cap affixed with Ag^+/Ag^+Cl^- electrodes (EasyCap, Herrching-Brieibrunn, Germany) in accordance with the 10-10 system (Chatrian et al, 1985). An electrode placed on the nose served as a reference and a ground electrode was positioned between FP_Z and F_Z sites. Vertical (VEOG) and horizontal (HEOG) electrooculographic activity was measured using two electrodes above and below the right eye as well as two electrodes positioned on the external canthus of both eyes. Electrode impedances were maintained below 5 kΩ, and electrical activity was recorded using a Brain Vision Amplifier® (Brain Products, Germany) with bandpass filters set at 0.1-120 Hz, digitized continuously at 500 Hz by Brain Vision Recorder Software (Brain Products, Germany).

3.6.8. ERP processing

Raw EEG signals were digitally filtered using Brain Vision Analyzer 2 (Brain Products, Germany) using 0.1 - 20 Hz bandpass filters. For the standard and each of the 5 deviants, epochs of 500 ms duration (including 100 ms pre-stimulus onset) were ocular corrected for eye movement and blink activity (Gratton et al, 1983). Artifacts (voltages ± 75 μV)

were excluded from analysis. Segments were baseline corrected to 50 ms pre-stimulus activity. Averages for the standard and each of the 5 deviant types were computed at each electrode site. MMNs were analyzed with difference waveforms derived via digital point-by-point subtraction of the standard stimulus values from those elicited by each of the deviant stimuli. MMN amplitude was measured as the most negative peak between 120-250 ms. MMN amplitude and latency were measured at F_Z. In order to determine of drug effects were specific to MMN, or to non-deviance detection mechanisms, the N100 component was measured at Fz, defined as the most negative peak between 90 and 120 ms after standard onset.

3.6.9. Analysis

Data was analyzed using IBM SPSS software. In order to limit Type I statistical errors, analysis was limited to MMNs derived from F_Z where amplitude is maximal. Whole group analysis (N = 24) utilized separate repeated measures analysis of variance (ANOVA) for each of the five deviant types, with drug condition as a within group factor. Because of the "inverted U" actions of nicotine, which has been shown to depend on baseline (placebo) MMN amplitudes (Knott et al, 2014a) a secondary repeated measures analysis was carried out by creating two sub-groups, High (N = 12) and Low (N = 12) for each deviant type, using a median split based on baseline (placebo) MMN amplitude, with drug condition as a within-subject factor and Low/High group as a between-subject factor. Significant Greenhouse-Geisser corrected interactions were followed up with t-tests. In order to specifically assess the differential effects of drug

condition on High vs. Low baseline groups, with the low baseline group serving as our laboratory model of schizophrenia, planned comparisons were made regardless of significant group by drug interactions. The Shapiro-Wilk test of normality was used for all datasets prior to analysis. Datasets that were not normally distributed were compared using the Wilcoxon signed rank test; all other data were compared with paired sample t-tests.

3.7. Results

3.7.1. Tests of normality

Shapiro-Wilk tests revealed non-normal distribution of amplitude values in the low baseline group for Duration (PP and MP), and Gap (PP). Non-normal distributions in the high baseline group for Gap (PP and PNic), Location (PP, PNic), Intensity (MNic), and Frequency (PP).

3.7.2. MMN Amplitudes

Table 3.1: Average MMN amplitudes for Overall (N = 24) and Low and High subgroups (N = 12).

		Total Mean Amplitude μV(± SE)	Low Group Mean Amplitude μV (± SE)	High Group Mean Amplitude μV (± SE)
Duration	PP	-1.86 (.26)	-0.96 (.36)	-2.75 (.12)
	MP	-2.28 (.25)	-2.33 (.31)	-2.24 (.40)
	PNic	-2.37 (.22)	-1.96 (.33)	-2.77 (.24)
	MNic	-2.06 (.28)	-1.43 (.40)	-2.69 (.31)
Gap	PP	-1.69 (.21)	-0.98 (.20)	-2.41 (.21)
	MP	-1.24 (.24)	-1.25 (.27)	-1.23 (.41)
	PNic	-1.57 (.29)	-1.25 (.44)	-1.88 (.37)
	MNic	-1.39 (.21)	-1.43 (.32)	-1.34 (.30)
Location	PP	-2.1 (.26)	-1.13 (.25)	-3.07 (.24)
	MP	-2.38 (.24)	-2.11 (.36)	-2.65 (.31)
	PNic	-2.19 (.22)	-1.63 (.30)	-2.74 (.22)
	MNic	-1.69 (.27)	-1.47 (.37)	-1.91 (.41)
Loud	PP	-2.77 (.32)	-1.61 (.35)	-3.93 (.23)
	MP	-3.03 (.32)	-2.51 (.42)	-3.54 (.45)
	PNic	-2.59 (.27)	-2.15 (.36)	-3.03 (.35)
	MNic	-2.59 (.32)	-1.60 (.33)	-3.58 (.37)
Frequency	PP	-2.3 (.26)	-1.38 (.25)	-3.23 (.26)
	MP	-2.46 (.36)	-2.19 (.33)	-2.74 (.66)
	PNic	-2.11 (.36)	-1.81 (.49)	-2.42 (.53)
	MNic	-2.25 (.31)	-1.65 (.41)	-2.85 (.43)

Average amplitudes are shown in Table 3.1. For each deviant, no overall (N = 24) drug effects were observed. The following sections describe results after subgrouping into low (N = 12) and high (N = 12) baseline MMN.

3.7.3. Subgroups

Direction of effects for each deviant in each subgroup are summarized in Table 3.2 and shown in Figure 3.1.

Table 3.2: Main effects and planned comparison directions for each subgroup.

	Main effect of Group?	Group x Drug Interaction?	Subgroup	Planned Comparisons
Duration	Yes	Yes	Low	PP < MP, PP < Pnic
			High	None.
Gap	No	No	Low	None.
			High	PP > MP, PP > Pnic, PP > MNic
Location	Yes	Yes	Low	PP < MP, MNic < MP
			High	PP > MNic
Intensity	Yes	No	Low	None.
			High	PP > Pnic
Frequency	Yes	No	Low	None.
			High	None.

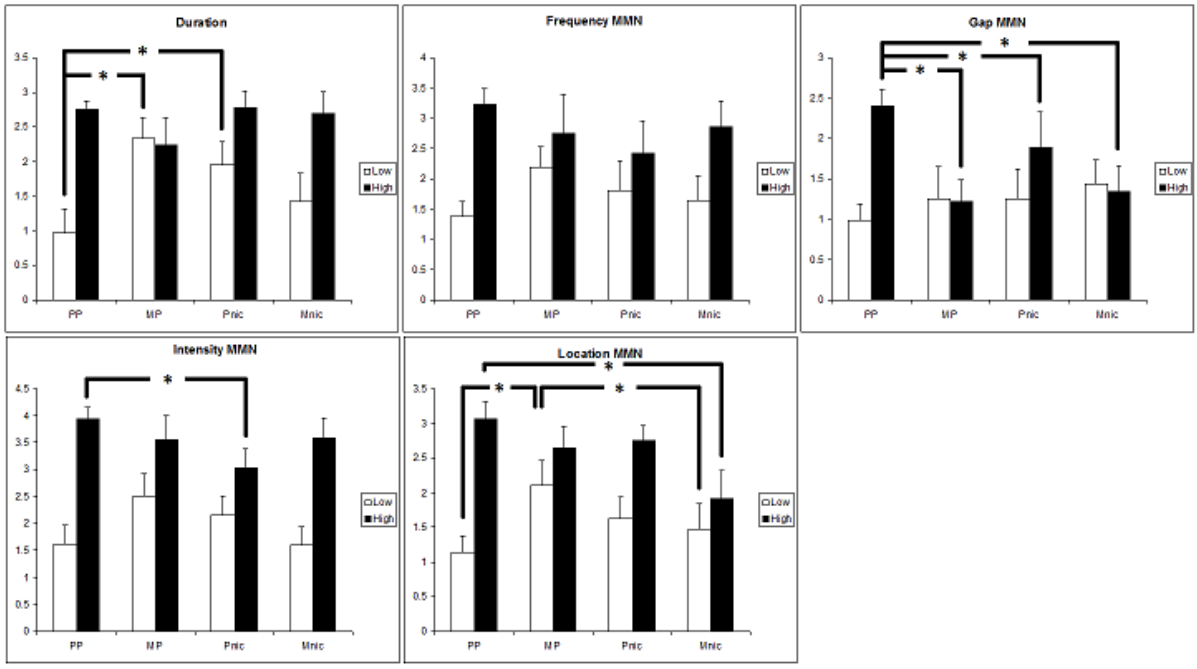

Figure 3.1: Low group (N= 12, white) and High Group (N = 12, black) amplitude values (μV) for each drug condition PP=placebo/placebo, MP = moclobemide/placebo, PNic = placebo/nicotine, MNic = moclobemide/nicotine. Significant group differences (Low vs. High) are not shown.

3.7.3.1. Duration

Low Group amplitudes and topographies are shown in Figure 3.2 (left). There was a significant effect of group [$F(1,22) = 13.531$, $p = .001$] and group by drug [$F(2.681, 58.972) = 3.430$, $p = .027$] interaction. Planned comparisons revealed significant differences in the low baseline group where PP amplitudes (M = -.960 μV, SE = .27) were smaller than both MP amplitudes (M = -2.33 μV, SE = .36) $Z = -2.28$, $p = .023$ and PNic amplitudes (M = -1.96 μV, SE = .29) $Z = -2.28$, $p = .023$. No significant differences were observed in the high baseline group.

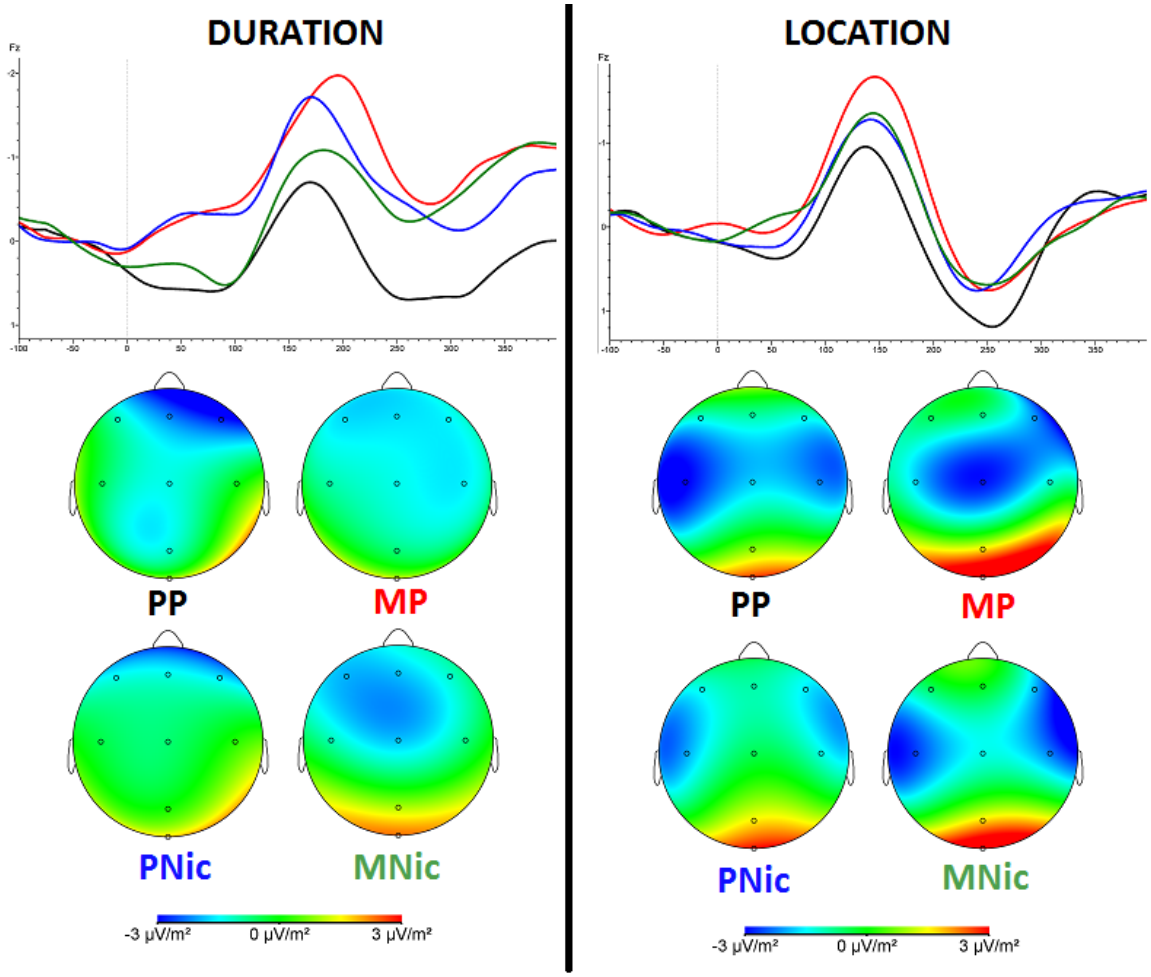

Figure 3.2: Low group (N = 12) grand averaged waveforms for duration and location deviants (Black = PP; Red = MP; Blue = PNic; Green = MNic) and topographic distributions at maximal MMN amplitudes.

3.7.3.2. Gap

No significant group or group by drug effects were observed. Planned comparisons revealed no differences between drug conditions in the low baseline group. In the high baseline group, PP (M = -2.41, µV, SE = .21) amplitudes were significantly larger than the MP (M = -1.23 µV, SE = .41) Z = -2.12, p = .034, PNic (M = -1.88 µV, SE = .37) Z = -2.04, p = .041, and MNic (M = -1.34 µV, SE = .30) Z = -2.51, p = .012 groups.

3.7.3.3. Location

Low group amplitudes and topographies are shown in Figure 3.2 (right). There was a significant effect of group [F(1,22) = 10.974, p = .003] and group by drug [F(2.805, 61.716) = .028] interaction. Planned comparisons in the low baseline group revealed significantly smaller amplitudes in the PP group (M = -1.13 μV, SE = .25) compared to the MP group (M = -2.11 μV, SE = .36) t = 2.45, p = .032, as well as larger amplitudes in the MP group compared to the MNic group (M = -1.50 μV, SE = .37) t = - 2.31, p = .041. In the high baseline group, higher amplitudes were observed in the PP group (M = -3.07 μV, SE = .24) compared to the MNic group (M = -1.91 μV, SE = .41) Z = -2.20, p = .028.

3.7.3.4. Intensity

There was a significant effect of group [F(1,22) = 23.596, p < .00] but no group by drug interaction. Planned comparisons in the high baseline group revealed significantly larger amplitudes in the PP group (M = -3.93 μV, SE = .23) compared to the PNic group (M = -3.03 μV, SE = .36) t = -2.32, p = .040.

3.7.3.5. Frequency

There was a significant effect of group [F(1,22) = 5.412, p = .030] but no significant group by drug interaction. Planned comparisons revealed no significant differences between drug conditions for either the low or high baseline groups.

3.7.4. MMN Latency

No significant group or group by drug interactions were observed for MMN latency in the overall group (N = 24) or the Low and High subgroups.

3.7.5. N100 Amplitude

No significant group or group by drug interactions were observed for N100 amplitude in the overall group (N = 24) or the Low and High subgroups.

3.7.6. Adverse Events

There was a significant effect of drug F(1,23)=1.643, p=0.033, due to higher severity ratings for symptoms in the PNic session (M=1.33, SE=0.00) compared to the PP session (M=1.00, SE=0.00) t(23)=0.23, p=0.029 as well as compared to the MNic session (M=1.00, SE=0.00) t(23)=0.23, p=0.029.

3.8. Discussion

The present study was designed to investigate the separate and combined effects of acute nicotine administration and MAO-A inhibition via moclobemide on the MMN event-related potential. As expected, there was no effect of nicotine, on the overall (N=24) group, likely due to the baseline dependencies of nicotine, which modulates the MMN in different directions depending on whether participants exhibit high or low MMN amplitudes in response to placebo. MAO-A inhibition did not affect the MMN in the overall group, either separately or combined with nicotine, as was expected and is consistent with previous studies showing no change in MMN after non-MAO modulation of MMN substrates (Leung 2007; 2010).

After subgrouping into High and Low baseline groups based on placebo MMN amplitude, nicotine increased amplitude in the low group for duration deviants, consistent with previous findings (Knott et al, 2014a). However, this previous study also found Low group improvement by nicotine in gap and location deviants, which were not replicated presently. It is possible that the smaller sample size in the current study (24 vs 60) as well as differences in stratification, where the previous study used three (Low, Medium, and High) baseline groups as opposed to two (Low and High) groups, allowed for targeting of more specifically low amplitude individuals. However, this is not supported by differences between studies in mean amplitude in gap deviant (present: -0.98 μV vs. previous: -1.20 μV) and location deviant (present: -1.13 μV vs. previous: -2.04 μV) which indicates that our current sample's low baseline group was actually more deficient in MMN amplitude. More likely, the high test-retest reliability of the duration deviant (Tervaniemi et al, 1999) makes it a more reliable measure of drug effects, as well as the

lack of a significant group or group by drug interaction observed in the gap deviant of the current study. Therefore, while nicotine's effects on duration deviant appear to remain consistent across studies, further research will be required to truly elucidate nicotine's effects on location and gap deviants for individuals with low baseline MMN amplitude. High baseline individuals had significantly reduced MMN amplitudes by nicotine for Intensity deviants, as has been previously seen (Knott et al, 2014a). High group amplitudes of gap deviant were also attenuated by nicotine, a finding not previously reported, though lack of main effects may indicate the drug differences observed during planned comparisons of the gap deviant may not be statistically meaningful.

MAO-A inhibition via moclobemide in the absence of nicotine increased duration and location deviant amplitudes in the Low baseline subgroup. This results is surprising, as most previous studies do not indicate that modulation of MAO-A substrates has any effect on MMN, with the exception of serotonin reuptake inhibition via escitalopram (Oranje et al, 2008; Wienberg, 2009). It is possible that escitalopram and moclobemide are unique in their effects on MMN indexed sensory memory, with serotonin increase as the common mechanism. Although some studies have shown no improvement by moclobemide in memory tasks (Fairweather et al, 1993; Siepmann et al, 2004), positive effects on memory have been observed in depressed (Allain, et al, 1992) and elderly (Wesnes et al, 1989) individuals. The latter study also demonstrated moclobemide's effectiveness in antagonizing cognitive impairments resulting from scopolamine induced cholinergic blockade in healthy controls, a finding which might be particularly relevant to our sample, considering the duration MMN was also increased in response to nicotine in the Low group, perhaps suggesting suboptimal cholinergic activation in these individuals.

In the High group, only gap MMN was attenuated after MAO-A inhibition, albeit in the absence of a significant main effect.

The combination of MAO-A inhibition and nicotine did not improve MMN amplitude for any deviant in the low baseline group, and attenuated MMN in the high group for both gap and location deviants. This too is surprising, as we expected the opposite effect, where MAO-A inhibition would mimic the effects of chronic smoking in high baseline individuals (i.e. prevent MMN attenuation) and SZ in the low group (i.e. fail to prevent amplitude increase). In the duration deviant, where we expected to see this effect, baseline amplitudes compared to the MNic condition (-0.96 and -1.43, respectively) were not significantly different, and did not approach the relatively robust increase seen with both moclobemide and nicotine (-2.33 and -1.96, respectively). The lack of a synergistic effect in the combination (MNic) group is puzzling, especially in light of a previous study where an earlier auditory paradigm (P50 gating) was significantly improved in low baseline individuals but not after either MAO-A inhibition or nicotine individually (Smith et al, 2014). However, it is important to note that although we have interpreted our current Low group as our model of SZ-like auditory sensory memory deficit, there is no evidence that these individuals share any underlying processing deficits with SZ. Thus, it is possible that a challenge to either the monoaminergic or cholinergic system (via moclobemide/nicotine) in these healthy individuals creates an imbalance in the "inverted U" relationship between cholinergic and monoamine (particularly dopamine) activation as has been proposed in a number of computational models of SZ (Moxon et al, 2003; Rolls et al, 2008) with cholinergic input activating inhibitory GABAergic interneurons in key circuits of the hippocampus and

frontal cortex. In this regard, an increase in MMN amplitude might actually reflect "abnormal" (compared to baseline) processing, with the combination of MAO-A inhibition and nicotine restoring the dopamine/cholinergic balance previously observed under placebo. While High group MMN gap and location deviants were attenuated, the high test-retest duration deviant did not change significantly relative to placebo.

In smokers with or without psychiatric diagnosis, these findings may have implications for the relatively low success rate of smoking cessation attempts in individuals attempting to quit without treatment strategies (3-6%, Lemmens et al, 2008) where intensity of withdrawal symptoms has been reported to be inversely related to platelet MAO activity (Rose et al, 2001). It is possible that the underlying mechanisms of duration MMN, modulated presently by both nicotine and moclobemide, may contribute to smoking withdrawal symptoms including attention processing deficits (Kassel, 1997). Indeed, moclobemide has shown some effectiveness as a smoking cessation strategy (Berlin et al, 1995) albeit not at long-term (1 year) biochemically-verified follow-up. Finding the "balance" of nicotinic activation and monoaminergic modulation in smokers wishing to quit will be a challenging endeavour, due to the unclear reversal time of MAO inhibition in ex-smokers (Rose et al, 2001), and further research is required to elucidate the specific contributions of nicotine and MAO inhibition to withdrawal symptoms.

This study has several limitations, including use of median-split with a relatively small sample size. Median split is notorious for producing misleading results (MacCallum et al, 2002), possibly due to a regression to the mean in subsequent trials (Barnett et al, 2005). However, this method was deemed appropriate in the current study, due to the highly replicated, "inverted U" effects of nicotine in healthy controls (Smith et

al, 2014; de la Salle et al, 2013; Knott et al, 2010; 2013; 2014a; 2014b) as well as the high test-retest reliability of the duration MMN deviant (Tervaniemi, 1999). The use of Low baseline group as a model of auditory processing in SZ is intended solely as an exploratory "first step" in assessing constituents of smoking in the disease, as we intentionally screened out any psychiatric or family-related psychiatric diagnoses, and thus our sample shares presumably little genetic commonalities with SZ. Furthermore, our low group mean duration amplitude (M = -0.96) was actually lower than a previous analysis of chronic SZ patients (M = -1.61; Javitt et al, 2000) while acknowledging that raw amplitude comparisons across studies using auditory paradigms may not be meaningful, due to differences in laboratory equipment, stimuli, and processing techniques.

The main finding of this study was an increase by nicitone, as well as MAO-A inhibition via moclobemide, but not both, on the amplitude of duration MMN in individuals stratified for low baseline amplitude. However, differential effects of nicotine and moclobemide were observed depending on deviant type as well as baseline group. This study stands in contrast to the previous notion that modulation of MAO-A substrates, namely serotonin, dopamine and norepinephrine have no effect on MMN. Further study involving larger sample sizes and more directed hypotheses will be required to confirm these preliminary findings, as the present results may potentially influence our understanding of the nAChR and NMDAR mediated deficits associated with abnormal auditory processing in SZ.

CHAPTER 4

The separate and combined effects of nicotine and monoamine oxidase A inhibition on the P3a and P3b event-related potentials

4.1. Overview

This manuscript investigates the separate and combined effects of nicotine and moclobemide on the P3a and P3b ERPs. While these ERPs are also candidate biomarkers in SZ, they are particularly interesting in the context of the current thesis' smoking model because i) there is ample evidence that nAChRs contribute substantially to neural mechanisms of attention and ii) the P3a and P3b index two different types of attention, i.e. novelty processing and target processing, and each of these mechanisms seems to be differentially influenced by cholinergic and monoaminergic stimulation. The novelty P300 paradigm allows us to investigate these two attentional processes within the same task. Participants are once again stratified by baseline amplitude in order to elucidate any inverted-U type responses to each drug condition.

4.2. Statement of author contribution

The initial experimental design of this study was drafted by Verner Knott and Pierre Blier, with input by Dylan Smith. Participants were recruited, screened and given orientations by Dylan Smith, with psychological and pharmacological screenings also performed by Vadim Ilivitsky. Programming of experimental stimuli was completed by Derek Fisher and Dylan Smith. ERP recording/analysis, statistical analysis, writing of the manuscript and generation of figures was completed by Dylan Smith. All authors critically reviewed and approved the final manuscript. This study was supported by a University of Ottawa Medical Research Fund grant awarded to Verner Knott.

4.3. Title Page

The separate and combined effects of nicotine and monoamine oxidase A inhibition on the P3a and P3b event-related potentials.

Dylan M Smith[1,2] Ph.D.(cand.), Derek Fisher[3] Ph.D, Pierre Blier[1,2,4]MD, Vadim Illivitsky[4] MD, Verner Knott[1,2,4] Ph.D., C.Psych.

[1] University of Ottawa Institute of Mental Health Research, Ottawa, Ontario, Canada
[2] Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada
[3] Department of Psychology, Mount Saint Vincent University, Halifax, Nova Scotia, Canada
[4] Royal Ottawa Mental Health Centre, Ottawa, Ontario, Canada

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4.4. Abstract

While a wealth of research has examined nicotine's effects on attention, relatively few studies have considered the monoamine oxidase (MAO) inhibiting properties of tobacco smoke. The isoform MAO-A, which is robustly inhibited in chronic smokers, metabolizes dopamine, serotonin, and norepinephrine in the human brain, and may also affect attentional processing. In order to more accurately model the effects of chronic tobacco use, we pharmacologically inhibited MAO-A via 75 mg moclobemide in a sample of 24 healthy non-smoking human males, and assessed attention via the novelty P300 event-related potential (ERP) paradigm after chewing 6 mg nicotine gum. Four separate test sessions included placebo/placebo, moclobemide/placebo, placebo/nicotine, and moclobemide/nicotine. Relative to placebo/placebo, an increase in novelty P3a amplitude was observed in the placebo/moclobemide condition but not the moclobemide/nicotine condition. An increase relative to placebo/placebo in P3b amplitude during the placebo/nicotine condition was also not seen in the moclobemide/nicotine condition. Stratification of subjects via median split based on placebo amplitude revealed these drug differences to be limited to low baseline amplitude individuals. Low baseline P3b individuals also exhibited a P3b amplitude increase in the moclobemide/placebo session. Moclobemide also disrupted earlier ERPs, namely P2 and N2. This study shows that moclobemide and nicotine can modulate P300 indexed auditory attention, but not when both drugs are delivered in combination. Thus, transient, nicotine-induced cognitive improvements experienced by new smokers may diminish with chronicity due to the effects of smoking-induced MAO inhibition.

4.5. Introduction

Despite the continued prevalence of cigarette smoking in society, the psychopharmacological effects of tobacco use remain poorly understood. Attention, a core cognitive function, is highly influenced by activation of nicotinic receptors (nAChRs) in the brain (Poorthuis and Mansvelder, 2013). In laboratory settings, the P300 event-related potential (ERP) has been a useful tool for measuring temporally precise brain activity during attention tasks, and has served as a biomarker in schizophrenia, a condition associated with high smoking rates, nAChR dysfunction (Kumari and Postma, 2005) as well as P300-indexed deficits in attention (Bramon et al., 2004). Although nAChRs and attention appear to be linked, non-nicotine components of tobacco smoke have a robust inhibitory effect on brain monoamine oxidase (MAO), an enzyme responsible for modulating neurotransmitters such as dopamine (DA), serotonin (5-HT) and norepinephrine (NA) (Berlin and Anthenelli, 2001). Therefore, the nicotinic and MAO-inhibiting components of tobacco smoke may influence attention in different ways. As such, there is a need to investigate the separate and combined effects of nicotine and monoamine oxidase inhibition on P300-indexed attention in humans.

The effects of smoking on attention are associated with nicotine's influence at nAChRs in the brain. Animal studies have shown nAChR activation in the medial prefrontal cortex (mPFC) to be essential for proper functioning in cue detection and attention tasks (Bloem et al., 2014). In human studies, nicotine's effects on cognition seem to be largely baseline dependent (Perkins, 1999). Nicotine improves performance of individuals with cognitive impairment and/or tobacco dependence, and impairs performance in individuals with

already optimal cognition (Newhouse et al., 2004). Clinical populations with attention deficits have also shown improvement with nicotine, including Alzheimer's Disease (White and Levin, 1999), attention deficit hyperactivity disorder (Potter et al., 2008), as well as schizophrenia (Harris et al., 2004); a group which may uniquely benefit from nicotinic agonists due to a deficit in the α7 nAChR (Freedman et al., 1995).

The baseline dependency of nicotine's cognitive effects has been well replicated using ERPs, such as the P300 paradigm (Knott et al., 2014b), which may be particularly useful for studying nicotine's effects on attention, as scalp recorded ERPs could potentially elucidate differences in attention that are not captured using discrete behavioural accuracy measures of neuropsychological tests (Polich, 2007). P300 is comprised of two different positive ERPs elicited at approximately 300 ms post-stimulus; the fronto-central P3a (also known as the novelty P300 if elicited in response to novel stimuli), which has been proposed to reflect redirection of attention towards novel, distracting sounds (Friedman et al., 2001), and the parietal P3b, which is elicited during target stimulus detection (Polich, 2007).

A recent meta-analysis showed diminished P3b amplitude in non-abstaining chronic smokers compared to non-smoking controls (Hedges and Bennett, 2014), and smoking deprivation reduced P3b amplitudes in a large sample of smokers (Evans et al., 2013), while acute smoking has been shown to increase P3a and P3b amplitudes (Polich and Criado, 2006). In non-smokers, some studies have shown no effect of nicotine on P3a (Knott et al., 2006; 2009, Evans et al., 2014), while others show reduced P3a amplitude in response to nicotine (Knott et al., 2011). P3b amplitude has been shown to be unaffected by nicotine (Lindgren et al., 1999; Evans et al., 2014). Such findings in non-

smokers may be explained by the baseline-dependant effects of nicotine, as small sample studies may only show effects of relatively high or low baseline individuals, while large sample studies may unintentionally average out any baseline-dependant effects by grouping high and low baseline P300 amplitude individuals together. When groups were divided by baseline P3b amplitude, nicotine increased P3b amplitudes in low baseline individuals and decreased P3b amplitudes in high baseline individuals (Knott et al., 2014b), with nicotine increasing P3a amplitudes in low baseline individuals in the same study.

While many studies focus primarily on nicotine's role in the modulation of attention, relatively few have taken into account the MAO inhibiting effect of tobacco smoke. The two human isoforms of MAO are inhibited via chronic tobacco smoke through the actions of β-carboline alkaloids (Herraiz and Chaparro, 2005); MAO-A is inhibted by ~28% and MAO-B by ~40% (Fowler et al., 1996a; 1996b). MAO-A, which metabolizes DA, 5-HT and NE, may be particularly important in attention due to its localization on cell bodies and in neurotransmitter projection areas (Finberg, 2014). MAO-A is selectively and reversibly inhibited by moclobemide, which has been shown to improve attention in depressed patients (Allain, 1992), as well as in a healthy control model of cholinergic deficit-induced cognitive decline via scopolamine (Wesnes et al., 1990).

ERP experiments suggest MAO-A activity has an effect on the P300. DA and NE; two MAO-A substrates, are theorized to be important for P300 generation (Polich, 2007). Moclobemide has been shown to reduce P3b latency, with no effect on amplitude, in depressed patients after 6 weeks of treatment (Wang et al., 2003). Comparisons of

healthy controls versus DA deficient individuals support a strong dopaminergic contribution to P3a generation, and a moderate contribution to P3b (Polich and Criado, 2006; Stanzione et al., 1991). DA antagonists have reduced P3a in healthy subjects (Kähkönen et al., 2002) and have modulated P3b amplitude in a baseline dependent manner (Takeshita and Ogura, 1994). Dexamphetamine, an indirect agonist of DA, NE and 5-HT decreased both P3a and P3b amplitudes in healthy subjects (Albrecht et al., 2011). Clonidine, a NE antagonist, decreased P3b amplitude in human and animal studies, (Joseph and Sitaram, 1989; Swick et al., 1994). The SSRI escitalopram did not affect P3b (Weinberg et al., 2009), and acute tryptophan depletion did not affect P3a (Ahveninen et al., 2002). Taken together, it seems that DA and NE are strong modulators of P300, with 5-HT having a lesser effect.

While nicotine and MAO-A substrates seem to modulate P300 indexed cognition, the specific interaction of nicotine with MAO-A inhibition is unclear. In the present study, we examined the effects of acute nicotine under conditions of MAO-A inhibition via moclobemide on the P3a and P3b in healthy males. Four experimental sessions included placebo/placebo (PP), moclobemide/placebo (MP), placebo/nicotine (PNic), and moclobemide/nicotine (MNic). Nonsmokers were used in order to avoid any confounding effects of smoking dependency. Previously, sensory gating indexed by the P50 ERP, a cognitive paradigm influenced by both DA-dependent signal-detection as well as cholinergic activation of GABAergic inhibitory interneurons (Moxon et al., 2003), was shown to be significantly improved in nonsmokers when nicotine was combined with moclobemide (Smith et al., 2014). In the present experiment, we utilized a paradigm in which infrequent target tones were intermixed with infrequent distracting novel sounds.

We hypothesized that P3a amplitudes elicited by detection of novel sounds would be most robustly influenced by MAO-A inhibition, due to an increase in DA-dependent signal detection. We further hypothesized that P3b amplitudes elicited by detection of target tones would be most robustly influenced by nicotine, due to an increase in cholinergic-dependent increase in attention. We hypothesized that the combination of MAO-A inhibition with acute nicotine would increase target-elicited P3b amplitudes while reducing P3a amplitudes elicited by the task-irrelevant novel sounds. As a secondary investigation, due to the baseline dependant effects of both nicotine and MAO-A substrates on P300, we hypothesized that drug effects would be more pronounced in individuals with low baseline amplitudes. We hypothesized an opposite effect, i.e. reduction of P3a and P3b amplitudes, in high baseline individuals.

4.6. Results

4.6.1 Behavioural accuracy

Table 4.1: Behavioural Accuracy measures by group. PP = placebo/placebo MP = moclobemide/placebo PNic = placebo/nicotine MNic = moclobemide/nicotine. FANov = False alarm in response to novel sound. FAStd = False alarm in response to standard tone. FATot = False alarm in response to either novel or standard sound.

Measure		Mean	Std. Error
Hits	PP	77.50	.943
	MP	77.96	.783
	Pnic	77.63	1.080
	Mnic	78.00	.704
Misses	PP	2.29	.914
	MP	1.96	.761
	Pnic	2.17	1.047
	Mnic	1.96	.675
FANov	PP	.46	.160
	MP	.50	.162
	Pnic	.42	.135
	Mnic	.21	.086
FAStd	PP	.92	.337
	MP	.88	.291
	Pnic	1.21	.517
	Mnic	.67	.243
FATot	PP	1.38	.367
	MP	1.38	.321
	Pnic	1.63	.518
	Mnic	.88	.289
RT	PP	1786.25	78.918
	MP	1743.16	66.633
	Pnic	1735.12	83.487
	Mnic	1743.01	67.333

Table 4.2: Amplitudes and latencies (± SE) for P3a and P3b ERPs for Total Group (N = 24) as well as Low baseline (N=12) and High baseline (N = 12) subgroups.

		Mean (± SE) μV	Low Group Mean (± SE) μV	High Group Mean (± SE) μV
P3a Amplitude	PP	11.44 (1.58)	5.91 (1.29)	16.98 (1.78)
	MP	13.68 (1.39)	9.31 (1.19)	18.03 (1.80)
	PNic	12.63 (1.36)	7.79 (1.23)	17.46 (1.42)
	MNic	11.58 (1.61)	6.31 (1.22)	16.85 (2.07)
P3a Latency	PP	331.08 (9.31)	333.50 (13.55)	318.42 (10.00)
	MP	334.08 (10.30)	340.67 (16.72)	318.92 (10.84)
	PNic	320.17 (8.84)	322.33 (13.77)	325.17 (8.81)
	MNic	318.33 (9.84)	321.83 (17.10)	328.75 (7.72)
P3b Amplitude	PP	13.92 (1.77)	7.71 (1.05)	20.13 (2.22)
	MP	16.19 (1.63)	11.58 (1.46)	20.80 (2.28)
	PNic	16.49 (1.62)	12.23 (1.36)	20.75 (2.41)
	MNic	15.30 (1.78)	10.19 (1.37)	20.41 (2.57)
P3b Latency	PP	373.58 (9.87)	369.67 (16.55)	377.50 (11.45)
	MP	389.42 (9.52)	385.00 (14.64)	393.83 (12.67)
	PNic	379.33 (7.65)	377.00 (13.78)	381.67 (7.34)
	MNic	382.83 (8.71)	380.17 (14.23)	385.50 (10.66)

Behavioural accuracy data is shown in Table 4.1. There were no significant drug effects for any behavioural accuracy measures, including Hits, Misses, False Alarms, False Alarms to the novel sound, False Alarms to the standard tone, and reaction time.

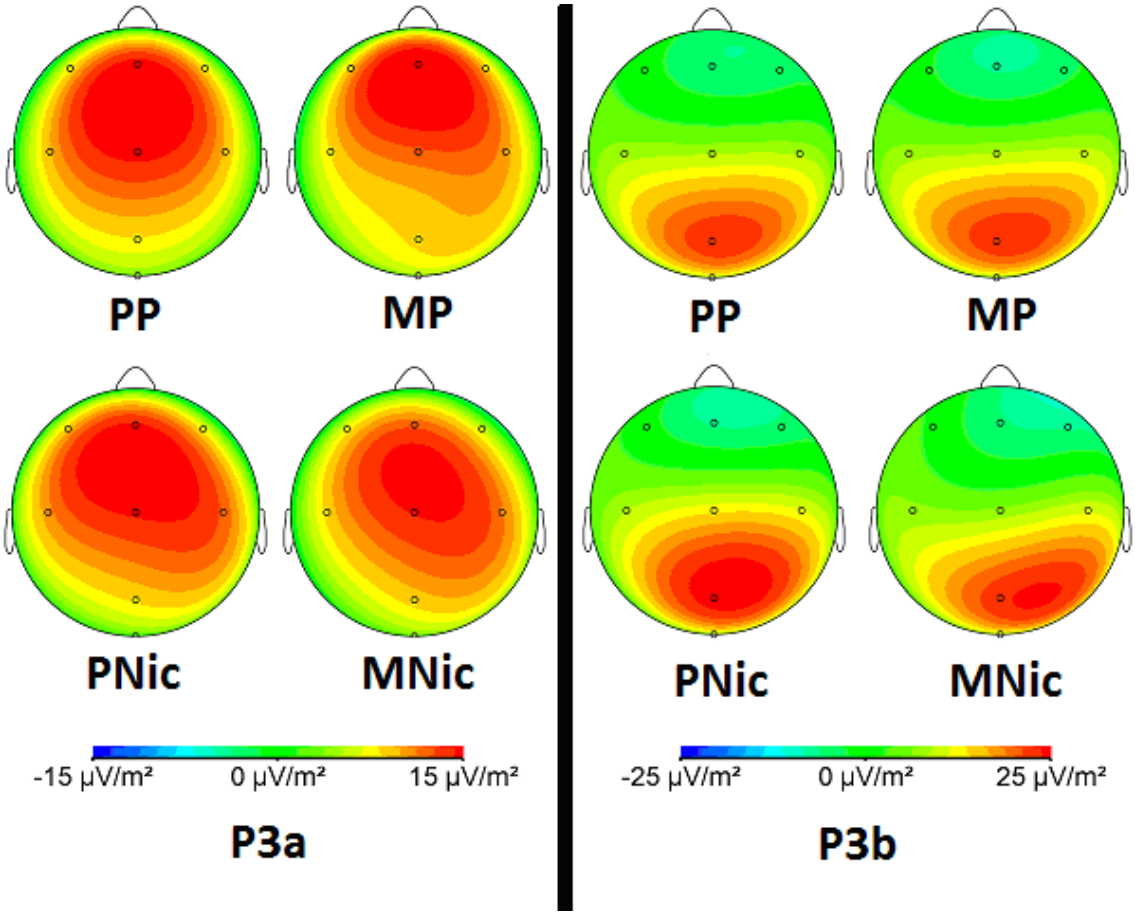

Figure 4.1: Current source density maps for each drug condition for P3a (left) and P3b (right).

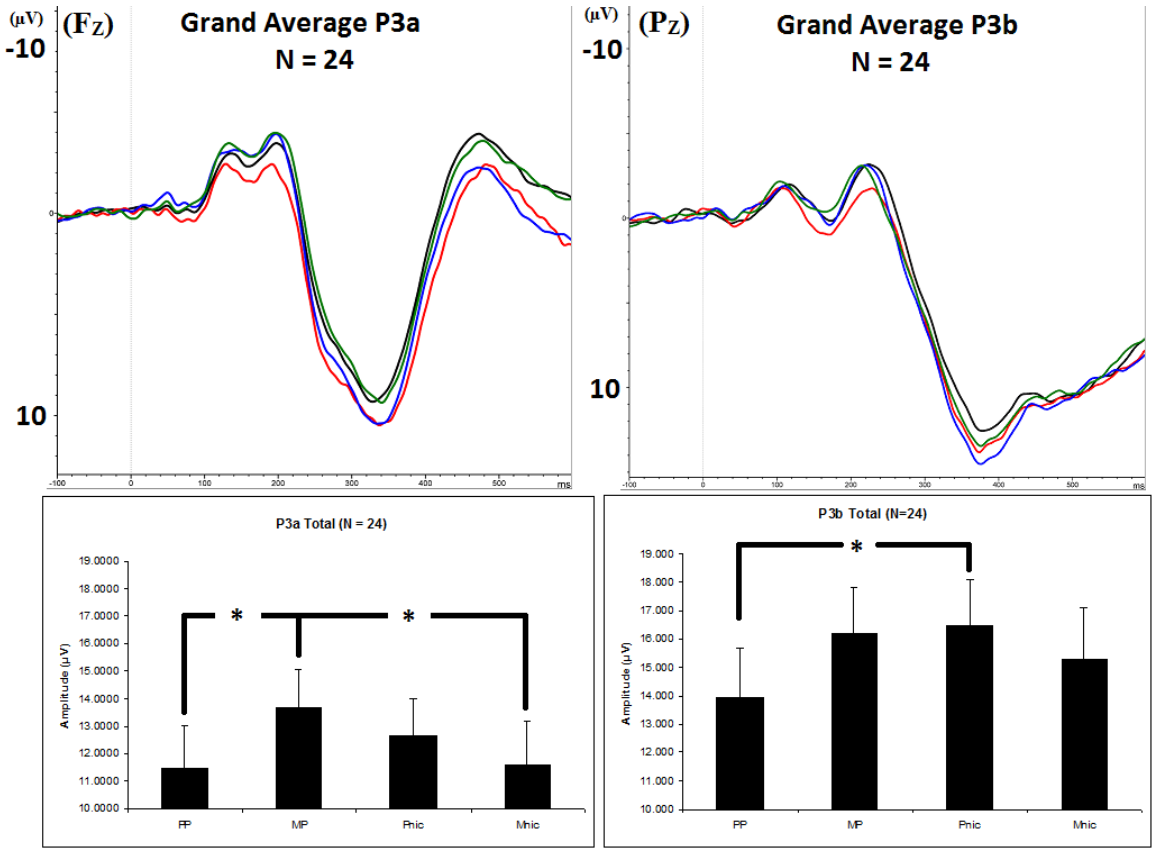

Figure 4.2: Total group (N=24) grand average waveforms and mean amplitudes (±SE) for P3a at Fz (left) and P3b at Pz (right). Black = PP, Red = MP, Blue = PNic, Green = MNic.

4.6.2. Novel stimulus ERPs

Grand average waveforms for P3a are shown in Figure 4.2 (left). No significant main effects were observed for P3a amplitudes or latency in the total group (N = 24) as well as the High and Low subgroups (N = 12 each). Planned comparisons revealed significantly larger P3a amplitudes in the MP condition (M = 13.68 μV, SE = 1.39) compared to the PP condition (M = 11.44 μV, SE = 1.58), t(23) = 2.25, p = .034, as well as compared to the MNic condition (M = 11.58 μV, SE = 1.61), t(23) = 3.38, p = .003. Planned

comparisons revealed no significant differences in P3a latency between individual drug conditions for either the High or Low baseline groups.

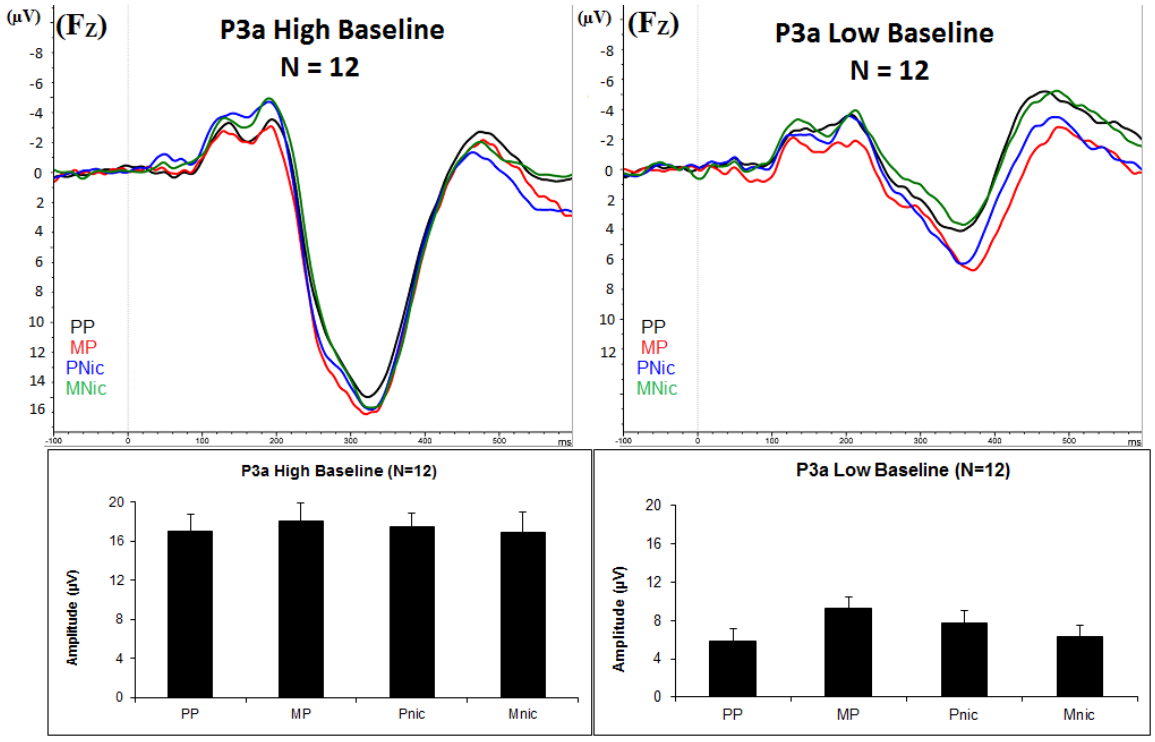

Figure 4.3: Grand average P3a waveforms and mean P3a amplitudes (±SE) for N = 12 High baseline individuals (left) and N = 12 Low baseline individuals (right). Black = PP, Red = MP, Blue = PNic, Green = MNic.

High and Low group P3a waveforms are shown in Figure 4.3. Planned comparisons in the Low baseline P3a group revealed higher P3a amplitudes in the MP condition (M = 9.32 μV, SE = 1.19) compared to the PP condition (M = 5.91 μV, SE = 1.29), t(11) = 2.40, p = .035, as well as compared to the MNic condition (M = 6.31 μV, SE = 1.22), t(11) = 4.46, p = .001. No significant differences were found between drug conditions in the High baseline P3a group.

Analysis of P2 amplitudes revealed a significant main effect of drug $F(3,66) = 2.98$, $p = .042$. Follow up comparisons revealed larger P2 amplitudes in the MP condition (M = .439 μV, SE = .59) compared to the PNic condition (M = -1.05 μV, SE = .54), $t = 2.41$, $p = .024$, as well as larger P2 amplitudes in the MP condition compared to the MNic condition (M = -1.05 μV, SE = .69), $t = 2.40$, $p = .025$. No significant effects were observed for P2 latency.

Comparisons in the Low baseline P3a group revealed significantly larger P2 amplitudes in the MP condition (M = .83 μV, SE = .74) compared to the PNic condition (M = -1.27 μV, SE = .82) $t(11) = 3.25$, $p = .008$. No significant differences were observed in the High baseline P3a group.

Analysis of N2 amplitudes revealed a significant main effect of drug $F(3,66) = 2.94$, $p = .040$. Follow up comparisons revealed larger N2 amplitudes in the PNic condition (M = -6.39 μV, SE = .94) compared to the MP condition (M = -4.68 μV, SE = .83), $t(23) = 2.44$, as well as larger N2 amplitudes in the MNic condition (M = -6.58 μV, SE = 1.04) compared to the MP condition $t(23) = 2.29$, $p = .032$. No significant effects were observed for N2 latency.

Comparisons in the Low baseline P3a group revealed significantly larger N2 amplitudes in the MNic condition (M = -6.73 μV, SE = 1.83) compared to the PP condition (M = -4.58 μV, SE = 1.36), $t(11) = 2.50$, $p = .030$, as well as larger N2 amplitudes in the PNic condition (M = -6.39 μV, SE = 1.40) compared to the MP condition (M = -3.40 μV, SE =

1.13), t(11) = 2.23, p = .048. No significant differences were observed between drug condition in the High baseline P3a group.

4.6.3. Target stimulus ERPs

Grand average waveforms for P3b are shown in Figure 4.1. There was a significant main effect of drug F(1,22) = 3.02, p = .040. Follow up comparisons revealed larger amplitudes in the MP condition (M = 16.19 µV, SE = 1.63) compared to the PP condition (M = 13.92 µV, SE = 1.77) t(23) = 2.25, p = .036, as well as larger amplitudes in the PNic condition (M = 16.49 µV, SE = 1.62) compared to the PP condition t(23) = 2.89, p = 0.008. No significant main effects or interactions were observed for P3b latency.

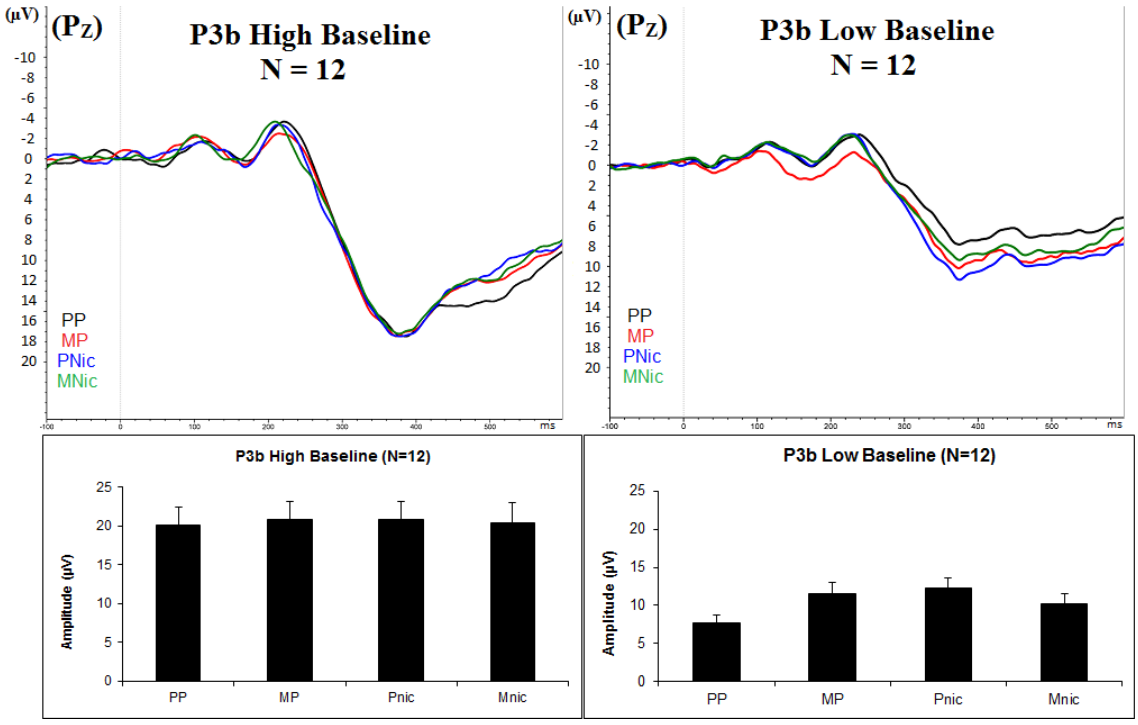

Figure 4.4: Grand average P3b waveforms and mean P3b amplitudes (±SE) for N = 12 High baseline individuals (left) and N = 12 Low baseline individuals (right). Black = PP, Red = MP, Blue = PNic, Green = MNic.

High and Low group waveforms are shown in Figure 4.4. Planned comparisons in the Low baseline group revealed significantly larger amplitudes in the MP condition (M = 11.58 μV, SE = 1.46) compared to the PP condition (M = 7.71 μV, SE = 1.05), t(11) = 2.36, p = .038 as well as larger amplitudes in the PNic condition (M = 12.23 μV, SE = 1.36) compared to the PP condition, t(11) = 4.00, p = .002. Amplitudes in the MP group were significantly larger than the MNic group (M = 10.19 μV, SE = 1.37) t(11) = 2.24, p = .046. No significant differences were observed between drug conditions in the High group. No significant differences were observed for P3b latency in either subgroup.

Analysis of P2 amplitudes revealed no significant main effects of drug or drug by group interaction. Pairwise comparisons showed no significant differences between individual drug conditions. Comparisons in the Low baseline P3b amplitude group revealed significantly larger P2 amplitudes in the MP condition (M = 2.27 μV, SE = .82) compared to the PNic condition (M = .53 μV, SE = .66) t(11) = 2.94, p = .013, as well as compared to the MNic condition (M = .22 μV, SE = .77) t(11) = 2.80, p = .017. No significant differences between drug groups were observed in the High baseline P3b amplitude group.

Analysis of N2 amplitudes revealed no significant main effects of drug or drug by group interaction. Pairwise comparisons revealed significantly larger N2 amplitudes in the PP condition (M = -4.95, SE = .71) compared to the MP condition (M = -3.33 μV, SE = .75), t(23) = 2.63, p = .015. Comparisons in the High baseline P3b amplitude group revealed significantly higher N2 amplitudes in the PP condition (M = -5.77 μV, SE = .91)

compared to the PNic condition (M = -4.33 μV, SE = .96), t(11) = 2.22, p = .049. Comparisons in the Low baseline P3b amplitude group revealed significantly larger N2 amplitudes in the PNic condition (M = -3.90 μV, SE = 70) compared to the MP condition (M = -2.24 μV, SE = 1.15), t = 2.28, p = .044.

4.7. Discussion

This study investigated the separate and combined effects of nicotine and MAO-A inhibition via moclobemide, on the auditory P3a and P3b in healthy non-smokers. In the present sample, moclobemide increased P3a amplitude compared to placebo, and nicotine increased P3b amplitude compared to placebo. After stratifying participants based on placebo amplitude, moclobemide increased P3a amplitudes compared to placebo in low-baseline P3a individuals. Both nicotine and moclobemide, when administered individually, increased P3b amplitudes in low-baseline P3b individuals, while the combination of moclobemide and nicotine did not. In high-baseline individuals, no drug effects were observed. No drug effects on P3a or P3b latency were observed both the total and stratified groups. To our knowledge, this is the first study to simultaneously investigate the effects of nicotine and MAO-A inhibition on the auditory P300 ERP.

The specificity of drug effects, i.e. moclobemide's influence of P3a and nicotine's influence of P3b, may result from the differential processing demands of these two stimuli within the experimental paradigm. Cholinergic activation is associated with sustained attention in stimulus-detection tasks (Sarter et al., 2001), and thus it is likely that nicotine preferentially improved processing of the task-relevant auditory stimuli in

the present study, indexed by an increase in P3b amplitude. Meanwhile, DA hyperactivity is associated with increased neuronal "gain", a state where depolarization of pyramidal neurons overrides inhibitory GABAergic inhibition (Lodge and Grace, 2011). Thus, in our sample, a moclobemide increase in synaptic DA may have favoured processing of the task-irrelevant distracting stimuli. Interestingly, the moclobemide-induced increase in P3a amplitude was significantly decreased to levels similar to placebo when moclobemide was combined with nicotine, suggesting that nicotine provided the compensatory cholinergic activation of GABAergic inhibitory neurons required to reduce the increase in neuronal gain caused by MAO-inhibition.

This specificity of effect found in our healthy controls may be relevant to clinical populations with high smoking rates, such as schizophrenia, where nicotinic stimulation has been targeted as a treatment pathway for patients (Olincy and Freedman, 2012). Transient cognitive improvements by nicotine experienced by patients during smoking onset may be lost in a shift to chronic smoking as MAO-A inhibition increases, requiring smokers to extract more nicotine in order to counter-act higher levels of synaptic monoamines. The drug effects shown in our healthy controls, including both improvement of attention by nicotine, and increased sensitivity to distracting sounds by MAO-inhibition, may be further magnified in clinical populations with cognitive deficits. A recent multi-site study found attenuated P3b amplitudes in patients with schizophrenia compared to controls, and smoking status was associated with reduced P3b amplitudes in controls but not patients (Turestky, 2015), suggesting that the increased synaptic DA achieved via chronic smoking-induced MAO-inhibition might emulate DA dysregulation associated with schizophrenia in attention tasks.

The lack of effect of nicotine on P3a amplitude in our total group is consistent with previous studies (Knott et al., 2006; 2009, Evans et al., 2014). However, no nicotine effects were observed in either high or low subgroups, which is inconsistent with a recent study that found P3a amplitude to be increased by nicotine in individuals with low baseline amplitudes (Knott et al., 2014b). In this previous study, however, participants were divided into low, medium and high baseline subgroups; the median split employed in the current study may have obscured nicotine's effects by including participants who might better be categorized in a medium baseline grouping. The observed increase of P3a amplitude by moclobemide is likely due to an increase in dopamine availability, as its generators reside in the anterior cingulate cortex and orbitofrontal cortex (Friedman et al., 2001), which are core anatomical regions in the dopamine-driven frontal attentional network (Polich and Criado, 2006). There was a lack of effect of drug condition on P3a latency, consistent with previous results (Knott et al., 2014b).

P3b amplitude was shown to increase following nicotine in our total sample. This contrasts with previous work that showed no effect of nicotine on P3b in nonsmokers (Lindgren et al., 1999; Evans et al., 2014). However, sub-grouping based on baseline (placebo) P3b revealed that improvements in P3b amplitude in our sample was limited to low baseline amplitude individuals, a method not used in previous studies and which may have averaged out any perceivable nicotine effects on P3b amplitude in these previous reports. Indeed, our results are consistent with a previous finding showing a nicotine-induced P3b amplitude increase in low baseline nonsmokers (Knott et al., 2014b), however, this study also found P3b amplitude decrease following nicotine in the high baseline group, which was not observed in our sample. It is possible that our smaller

sample size was comprised of a greater proportion of individuals with low baseline amplitudes and thus did not elucidate strong effects on both sides of the median split. Interestingly, our low baseline group also exhibited increased P3b amplitudes in the moclobemide condition, but not in the combination nicotine+moclobemide condition. The P3b improvement in low baseline individuals by moclobemide is consistent with one study that found baseline effects of sulpiride on P3b amplitude (Takeshita and Ogura, 1994), and further supports a low-baseline skewing of our present sample. Thus it seems in individuals with low baseline P3b amplitude, both nicotine or moclobemide can improve P3b indexed attention to auditory targets. No effects were observed for P3b latency, consistent with previous results (Knott et al., 2014b).

The lack of drug effect on task performance suggests the task used in the present study may have been too easy for a healthy control sample. Previous studies have shown that nicotine may differentially affect P300 depending on task difficulty (Le Houezec et al., 1994), and thus future studies may benefit from adjusting task parameters to induce a higher cognitive demand in healthy controls, possibly more accurately recreating the psychological conditions of clinical and/or smoking populations.

Post-hoc analysis showed increased P2 amplitudes and decreased N2 amplitudes in the moclobemide condition, compared to the nicotine and combination conditions, though visual inspection of the grand average waveforms (Figures 4.1, 4.2, and 4.3) suggests these effects stem from a shift towards greater positivity by moclobemide in this early latency range, particularly in low P3a and P3b baseline individuals. The N2 has been shown to be decreased in chronic smokers (Buzzell et al., 2014) thus it is possible that MAO inhibition in chronic smoking individuals is responsible for irregularities in these

early auditory processing ERPs. A moclobemide-induced decrease in the dopaminergic signal-to-noise ratio may attenuate early processing of incoming sounds.

This study has several limitations, including a small sample size combined with a median split which further reduced power in subgroup analyses. The use of median split reduces statistical power, and may lead to repeated measures regressing to the mean in consecutive trials (Barnett et al., 2005), however, this method was deemed appropriate for the current study due to the established "inverted U" relationship between nicotine and cognition (Smith et al., 2014; Knott et al., 2014b), where the high test-retest reliability of the P300 (Hall et al., 2006) is expected to elucidate true drug effects in subsequent sessions. However, more accurate results may have be obtained by using multiple sessions for each drug condition. While this study used a single dose of moclobemide, it is expected that a multi-dose regimen would more accurately model MAO-A inhibition in chronic smoking, due to an expected first-pass effect of moclobemide (Hoffman-Laroche, 2009). As this study was limited to scalp recorded potentials from eight electrodes, we are unable to determine the precise neural mechanisms, associated with the observed drug effects. Further study would benefit from high resolution imaging techniques as well as plasma analysis in order to establish a mechanism of action in which nicotine and moclobemide exert their effects on auditory attention. Furthermore, the present study was limited to MAO-A inhibition, and as such, in order to more accurately model the effects of chronic tobacco use, a combination of MAO-A and MAO-B inhibition is required in future research.

4.7. Conclusion

This study showed an increase in target-detection via nicotine, and an increase in distracter processing via moclobemide. Therefore, transient improvements in attention perceived by smokers may eventually lead to increases in distractibility when chronic smoking induces significant brain MAO inhibition. Drug effects were found to be most robust in individuals with low-baseline amplitudes. Therefore, individuals with baseline cognitive deficits, such as schizophrenia patients, may be more susceptible to the attention-modulating effects associated with cigarette smoking.

4.8. Experimental Procedure

4.8.1. Study Participants

Twenty-four healthy right handed males were recruited through local advertisement, and screened via self-report for psychiatric disorder, including, past, or 1st degree relative family associations, head trauma/seizure, medication use, excessive caffeine use (> 4 cups / day), and body mass index (BMI = 20-30 kg/m^2). Participants were administered the structured clinical interview for DSM-IV-R Non-Patient Edition (SCID-NP: First et al., 1995), the Family Interview for Genetic Studies (FIGS: Maxwell 1992), and assessment for normal hearing. Participants were self-reported non-smokers, defined as having smoked less than 100 total lifetime tobacco products, and none in the past year. Smoking status was confirmed on each session via expired carbon monoxide (CO) levels (< 3ppm).

4.8.2. Experimental Design

On four separate days, separated by a minimum 48 hours, participants were administered drug combinations including placebo/placebo (PP), moclobemide/placebo (MP), placebo/nicotine (PNic), or moclobemide/nicotine (MNic) in a randomized, double-blind, placebo-controlled crossover design. This study was approved by and carried out in compliance with the Royal Ottawa Health Care Group Research Ethics Board and the University of Ottawa Research Ethics Board.

4.8.3. Moclobemide administration

Prior to study participation, participants were interviewed by the study physician to screen for any contraindications associated with the use of moclobemide. 75 mg moclobemide (Manerix®, Hoffman-La Roche) was administered on non-placebo sessions. Moclobemide has a Tmax of 49 minutes and a 1.5 hour elimination half-life, and has been shown to decrease plasma 2,5-dihydroxyphenylglycine (DHPG), a measurement of MAO activity, by ~55% at 120 min (Hoffman-La Roche Ltd, 2009), and thus a 75 mg dose was used in order to attain ~ 30-40% plasma DHPG reductions similar to what has been observed in chronic smokers (Fowler et al., 1996[a]). Both moclobemide and placebo (cellulose) were administered in opaque capsules.

4.8.4 Nicotine administration

6 mg cinnamon flavoured Nicorette® (Johnson & Johnson Inc., Markham, Ontario, Canada) gum was administered via 2 pieces (4 mg + 2 mg) and chewed in accordance with manufacturer's guidelines, i.e., chewing for 25 minutes total, with two bites per minute (as cued by audio recording), and "parking" gum between the teeth and cheek between bites. This method yields peak blood nicotine levels at approximately 30 minutes proceeding initial chewing with an elimination half-life of ~120 min (Le Houezec, 2003) and was used to achieve similar blood-nicotine levels to that of an average smoker after a single cigarette of average nicotine yield, i.e., 15-30 ng/ml (Hukkanen et al., 2005). Participants wore a nose plug while chewing in order to reduce any perceivable differences between nicotine and placebo (also cinnamon flavoured) gum.

4.8.5. Study procedure

All tests sessions were conducted between 9:00am and 1:00pm after 8 hours of abstinence from food, alcohol, and caffeine. Participants were administered a capsule containing either 75 mg moclobemide or placebo for oral ingestion, after which they engaged in light reading during a 90 minute rest period to ensure Tmax activity during ERP recording. Electrodes were attached during the end of the rest period while the participant chewed nicotine or placebo gum. The P300 paradigm was administered once the chewing session was complete.

4.8.6. P300 paradigm

During recording, participants were seated upright in a chair with their right hand on a response pad. Eight hundred sequential sounds were presented in total, divided into four blocks, with 80% of tones being standard, 1000 Hz, 70 dB pure tones with 336 ms duration. 10% were target tones, distinguished by a lower frequency (700 Hz) and the remaining sounds consisted of novel non-target environmental sounds (e.g., baby cry; 169-399 ms, 65-75 dB; Kimbo et al., 2010; Friedman et al., 2001). Sounds were presented through headphones with an inter-stimulus interval of 1000 ms using Presentation software (Neurobehavioral Systems, Albany, CA, USA). Participants were instructed to press a button using their right index finger in response to the target tones only. Correct responses (with reaction time), missed targets, and false alarms were logged.

4.8.7. Electrophysiological recording

EEG was recorded from 8 scalp sites (F_Z, F_3, F_4, C_Z, C_3, C_4, P_Z, O_Z) via cap affixed with Ag^+/Ag^+Cl^- electrodes (EasyCap, Herrching-Brieibrunn, Germany) in accordance with the 10-10 system (Chatrian et al., 1985). A ground electrode was positioned between FP_Z and F_Z sites, and an electrode placed on the nose served as a reference. Vertical (VEOG) electrooculographic activity was measured using electrodes above and below the right eye, and horizontal (HEOG) activity was measured from electrodes placed on the external canthus of both eyes. Recording did not begin until all electrodes exhibited an impedance below 5 kΩ. Scalp activity was recorded using a Brain Vision amplifier and

Brain Vision Recorder software (Brain Products, Germany) with 0.1-120 Hz bandpass filters and digitized continuously at 500 Hz.

4.8.8. ERP processing

ERPs were processed using Brain Vision Analyzer 2 (Brain Products, Germany). Raw EEG signals were digitally filtered using a 0.1 - 30 Hz bandpass limit. Ocular activity was corrected in each channel (Gratton et al., 1983) and continuous EEG was segmented into 1100 ms epochs including a 100 ms pre-stimulus baseline. Artifact rejection excluded epochs containing EEG activity exceeding ± 75μV, and segments were baseline corrected using the 100 ms pre-stimulus activity. Target, deviant (P3b), and novel (P3a) sound epochs were averaged separately, with segments containing missed targets or false alarms excluded from the average. A minimum of 30 useable segments were required for statistical analysis, and all participant data met this requirement. P3a and P3b peak detection was based on grand averages (N = 24) for the novel and deviant sounds. P3a peaks were selected within 200-450 ms post-stimulus at Fz where it exhibited maximal voltage (Figure 4.4, left), and P3b was selected within 250-500 ms post-stimulus at Pz where it exhibited maximal voltage (Figure 4.4, right). Visual inspection of grand average waveforms revealed differences in N2 and P2 amplitudes and therefore, as a post-hoc analysis, N2 peaks were selected within 150-250 ms post stimulus for novel sounds, and within 200-300 ms post stimulus for target sounds. P2 peaks were selected between 100-200 ms post stimulus for novel sounds, and within 150-250 ms for target sounds.

4.8.9. Statistical Analysis

Data was analyzed using SPSS software (IBM Corp, Armonk, NY, USA). Whole group (N = 24) analysis utilized separate repeated measures analysis of variance (ANOVA) for P3a and P3b at the site of maximal activity only, as well as behavioural accuracy measures, with drug condition as a within group factor. Because of the baseline dependant, "inverted U" effects of nicotine on cognitive ERPs (Knott et al., 2014b), a secondary repeated measures analysis was performed after stratifying participants into two subgroups, via median split, based on ERP amplitude exhibited during the PP session. Different subgroups were created for P3a and P3b, based on their respective amplitudes. Repeated measures ANOVA for subgroups utilized drug condition as a within subject factor and Low/High group as a between subject factor. Significant Greenhouse-Geisser corrected interactions were followed up with paired samples t-tests. Drug x group effects were followed up regardless of significant interactions in order to verify our hypotheses on the baseline effects of each drug condition.

4.8.10. Acknowledgements

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CHAPTER 5

The Separate and combined effects of monoamine oxidase A inhibition and nicotine on resting state EEG

5.1. Overview

The past 3 chapters have focused on the effects of four drug conditions in auditory ERP paradigms. However, the pharmacological effects are not necessarily limited to processing of external stimuli. The default mode network, which describes activity within and between brain regions in the absence of external stimuli, is thought to be heavily influenced by the cholinergic system. Neural oscillations of various frequencies associated with default mode activity can be captured through recording of EEG while the participant is at rest in silence with eyes closed. This manuscript investigates the separate and combined effects of nicotine and moclobemide on resting state EEG, the results of which complements the findings in the previous chapters, by demonstrating the influence of each drug condition on various EEG frequency bands associated with arousal and cognition.

5.2. Statement of author contribution

The initial experimental design of this study was drafted by Verner Knott and Pierre Blier, with input by Dylan Smith. Participants were recruited, screened and given orientations by Dylan Smith, with psychological and pharmacological screenings also performed by Vadim Ilivitsky. ERP recording/analysis, statistical analysis, writing of the manuscript and generation of figures was completed by Dylan Smith. Derek Fisher made significant contributions to the interpretation of data. All authors critically reviewed and approved the final manuscript. This study was supported by a University of Ottawa Medical Research Fund grant awarded to Verner Knott.

5.3. Title Page

The Separate and combined effects of monoamine oxidase A inhibition and nicotine on resting state EEG

Dylan M Smith[1,2] B.Sc, Derek Fisher[3] Ph.D, Pierre Blier[1,2,4]MD, Vadim Illivitsky[4] MD, Verner Knott[1,2,4] Ph.D.

[1] University of Ottawa Institute of Mental Health Research, Ottawa, Ontario, Canada
[2] Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada
[3] Department of Psychology, Mount Saint Vincent University, Halifax, Nova Scotia, Canada
[4] Royal Ottawa Mental Health Centre, Ottawa, Ontario, Canada

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5.4. Abstract

While nicotine is often associated with the neuropsychological effects of tobacco smoke, the robust monoamine oxidase (MAO) inhibition observed in chronic smokers is also likely to play a role. Electroencephalographically (EEG) indexed alterations in baseline neural oscillations by nicotine have previously been reported in both smokers and nonsmokers, however, little is known about the effects of MAO inhibition in combination with nicotine on resting state EEG. In a sample of 24 healthy nonsmoking males, the effects of 6 mg nicotine gum, as well as MAO-A inhibition via 75 mg moclobemide, were investigated in separate and combined conditions over four separate test sessions. Drug effects were observed in the $alpha_2$, $beta_2$, and theta band frequencies. Nicotine increased $alpha_2$ power, and moclobemide decreased $beta_2$ power. Theta power was decreased most robustly by the combination of both drugs. Therefore, this study demonstrated that the nicotinic and MAO inhibiting properties of tobacco may differentially influence fast-wave oscillations ($alpha_2$ and $beta_2$), while acting in synergy to influence theta oscillations.

5.5. Introduction

The effects of tobacco smoke on the neuropsychological state of humans have been shown to be reflected in changes of oscillatory neural activity measured at the scalp through electroencephalography (EEG) during resting state (Roth and Battig, 1991). Such changes may index nicotine's effect on mood (Knott, 1991) and/or cognition (Mansvelder et al, 2006), possibly through modulation of default mode network activity (Tanabe et al, 2011; Beaver et al, 2011). While it is possible that the addictive effects of smoking are related to nicotine's amelioration of withdrawal-induced neuropsychological deficits in these domains (Heishman, 1999), few studies have investigated the role of monoamine oxidase inhibiting agents found in tobacco smoke in the modulation of neural indices of mood and cognition (Berlin and Anthenelli, 2001). Therefore, in order to accurately study the effects of chronic smoking, both nicotine and MAO inhibition, and their effect on neural oscillations at resting state, require investigation. Unfortunately, studies utilization smoking dependant populations are unable to differentiate "true" drug effects from those associated with alleviation of withdrawal (Levin et al, 2006), and therefore, there is a need to establish effects of nicotine and MAO inhibition on resting state EEG in non-smoking healthy controls.

Neural activity quantified by EEG frequency bands have been shown to reflect the summed activity of several large-scale brain networks, including influence from cortical and sub-cortical structures (Mantini et al, 2007). Although there is no one-to-one mapping of any given frequency band with a given neural structure or function, EEG oscillations have been associated with a number of cognitive processes (Herrmann et al,

2015). Alpha oscillations, predominantly observed in adults at rest with eyes closed (Simon and Emmons, 1956), have been associated with memory (Klimesch, 1997), attention (Hanslmayr et al, 2011) as well as top-down inhibition of responses during cognitive tasks (Klimesch et al, 2007). Beta oscillations are associated with cognitive processes responsible for maintaining/changing motor actions in sensorimotor cortex dependant tasks (Kilavik et al, 2013), as well as cognitive control and attentional effort (Stoll et al, 2015) during these tasks. Delta oscillations are largely associated with inhibition of thalamocortical inputs during attention tasks, and are thought to reflect inhibition by frontal cortex of task-irrelevant neural networks (Harmony, 2013). Theta oscillations are associated with hippocampus-dependant memory (Klimesch, 1999; Mitchell et al, 2008) and are also thought to contribute to frontal cortex directed inhibition (Huster et al, 2013). Although gamma oscillations have been associated with a number of cognitive processes such as declarative memory (Nyhus and Curran, 2010), it has recently been proposed that gamma oscillations reflect activation of cortical tissue and is not specific to any specific cognitive function (Merker, 2013).

In smokers, smoking an individuals' preferred brand of cigarette has been shown to result in reduction of slow wave delta (1.5 - 6.0 Hz) and theta (6.0 - 8.5 Hz) power, as well as increases in fast wave alpha (8.5-12.5 Hz) and beta (12.5-30.0 Hz) (Knott, 2001). Similar changes in EEG activation have been observed following nicotine administration via polacrilex (Pickworth et al, 1989), transdermal patch (Knott et al, 1999), nasal spray (Teter et al, 2002) and intravenous injection (Lindgren et al, 1999). However, these studies utilized abstaining smokers and thus the resultant EEG changes likely represent the combined effects of nicotine's activation/desensitization of nicotinic acetylcholine

receptors (nAChRs) in various brain regions, as well as a reversal of the neuropsychological state associated with smoking withdrawal symptoms (Domino et al, 2009). One recent study investigated the effect of 6 mg nicotine gum on resting EEG in nonsmokers and found increased alpha$_2$ (10.5 - 13 Hz) power at the left frontal scalp region compared to placebo gum (Fisher et al, 2012), and this supported a previous pilot study which administered nicotine via subcutaneous injection in 4 nonsmokers (Foulds et al, 1993).

Attempts at pharmacological modulation of the nicotine-EEG profile have targeted individual neurotransmitter systems. Haloperidol, a dopamine dopamine D_2 receptor antagonist, inhibited smoking-induced increase of beta power (Walker et al, 2001). Modulation of serotonin via acute tryptophan depletion did not influence the EEG profile after smoking (Perugini et al, 2003), nor did norepinephrine modulation via alpha-2-noradrenergic autoreceptor agonist clonidine (Knott et al, 2005). Glutamatergic modulation via the NMDA receptor antagonist ketamine decreased alpha, beta, and delta power in nonsmokers but not in smokers, and nicotine pretreatment did not alter this effect (Knott et al, 2006). Opioid receptor antagonist naltrexone prevented nicotine-induced decreases in delta and theta activity in abstaining smokers (Knott and Fisher, 2007). Thus it seems that nicotine's effects on EEG activation is differentially sensitive to modulation of dopamine and opioid transmission, but is not robustly affected by modulation of serotonin or norepinerphine.

While the neuropsychological effects of smoking are often attributed to nicotine, chronic smokers show robust inhibition of both isoforms of MAO. MAO-A is inhibited by ~28% (Fowler et al, 1996[a]) and MAO-B is inhibited by ~40% (Fowler et al, 1996[b])

through the actions of β-carboline alkaloids in tobacco smoke (Herraiz and Chaparro, 2005). MAO-A,which metabolizes serotonin (5-HT), norepineprhine, and dopamine (a common substrate with MAO-B), may contribute to the effects of smoking on resting EEG, as selective MAO-A inhibition via befloxatone has been shown to increase $alpha_1$ power in healthy volunteers (Luthringer et al, 1996). However, high doses of befloxatone also increased theta power, inconsistent with EEG profiles of smoking. Befloxatone has also been shown to increase beta power compared to placebo in elderly subjects (Patat et al, 1997). One interesting study examined the relationship between frontal midline theta activity and platelet MAO in healthy males (Hashimoto et al, 1988), and found a negative correlation between the two measures. This same study also found that individuals who scored high on measures of extroversion tended to exhibit higher theta activity and lower platelet MAO. Thus MAO activity may also play a role in the neuropsychological basis of personality, as well as cognition and default mode network activity.

It is possible that the effects of nicotine act in synergy with MAO inhibition in chronic smokers to produce a neural state associated with a characteristic EEG profile, however we are aware of no studies to date that have studied the combined and separate effects of nicotine and MAO inhibition on resting EEG. We hypothesized that, like nicotine, a 75mg dose of MAO-A inhibitor moclobemide would increase EEG indexed alpha power in human healthy nonsmokers, and that nicotine, when combined with MAO inhibition would increase alpha beyond the effects of either drug individually. While we expect no nicotine effects on theta activity, we hypothesized that MAO inhibition would increase theta activity and for nicotine to enhance this effect.

5.6. Methods

5.6.1. Study participants

Twenty-four healthy right handed nonsmoking males were recruited through local advertisement. Via self-report, participants were screened for personal and 1st degree family member psychiatric history, head trauma/seizure, medication use (including over-the-counter non-prescription medication as well as herbal medicine), excessive caffeine use (> 4 cups/day or the presence of withdrawal symptoms during caffeine abstinence), and body mass index (BMI = 20-30 kg/m^2). Only male participants were included in order to avoid any potentially confounding effects of menstrual cycle variation in serotonin levels (Hindberg and Naesh, 1992). All participants were non-smokers (< 100 total lifetime cigarettes / tobacco products and zero in the past year), which was confirmed on each session by measurement of expired carbon monoxide (CO) levels (< 3ppm). Each participant was interviewed prior to the study using the structured clinical interview for DSM-IV-R Non-Patient Edition (SCID-NP) (First et al, 1995) and the Family Interview for Genetic Studies (FIGS) (Maxwell 1992). Participants were also screened for hearing deficits via audiometric assessment.

5.6.2. Experimental design

This study was approved by and carried out in compliance with the Royal Ottawa Health Care Group Research Ethics Board and the University of Ottawa Research Ethics Board.

Prior to study participation, participants attended an orientation session including an explanation of study procedures and familiarization with lab equipment. Each participant attended the lab on four experiment days, separated by a minimum 48 hours. In a randomized, double-blind, placebo-controlled crossover design, participants were administered either placebo/placebo (PP), moclobemide/placebo (MP), placebo/nicotine (PNic), or moclobemide/nicotine (MNic) combinations.

5.6.4. Moclobemide administration

All participants were screened for any contraindications associated with moclobemide by the study psychiatrist. On non-placebo sessions, 75 mg moclobemide was administered orally in opaque capsules (cellulose was given in the same capsules during placebo sessions). Moclobemide, exhibiting a Tmax of 49 minutes and a half-life of 1.5 hours, has been shown to decrease plasma 2,5-dihydroxyphenylglycine (DHPG), a measurement of MAO activity, by ~55% at 120 minutes (Hoffman-La Roche Ltd, 2009). In this study, a 75 mg dose was used in order to attain ~ 30-40% MAO inhibition similar to levels observed in chronic smoking (Fowler et al, 1996[a]).

5.6.5. Nicotine administration

6 mg cinnamon flavoured Nicorette® (Johnson & Johnson Inc., Markham, Ontario, Canada) gum was administered via 2 pieces (4 mg + 2 mg). The participant was instructed to bite twice when cued via audio recording, and to "park" gum between teeth

and cheek between bites, in accordance with manufacturers guidelines. Total chewing time was 25 minutes. This method has been shown to yield peak blood nicotine levels at approximately 30 minutes proceeding initial chewing with an elimination half-life of ~120 minutes (Le Houezec, 2003) and was used to achieve similar blood-nicotine levels to a smoker after one cigarette of average nicotine yield, i.e., 15-30 ng/ml (Hukkanen et al, 2005). In order to eliminate any perceivable differences between nicotine gum and placebo (both cinnamon flavoured), participants wore a nose plug while chewing.

At the end of each session, severity of nicotine-related symptoms (Harkrider and Hedrick, 2005) was recorded, including self-reports of heart pounding, headache, dizziness, and nausea. Symptom severity was quantified on a five-point scale where 1 = no symptoms, 2 = mild symptoms, 3 = moderate symptoms, 4 = strong symptoms, and 5 = extreme symptoms.

5.6.6. Experiment procedure

All test sessions were conducted between 9:00 am and 1:00 pm on weekdays, after 8 hours of abstinence from food, medication, alcohol, and caffeine, with each of the four sessions beginning at the same time of day for each participant. After checking expired CO levels, opaque capsules containing either 75 mg moclobemide or placebo were administered orally, after which participants engaged in light reading during a 90 minute rest period to ensure Tmax activity during EEG recording. Nicotine gum was administered at the end of the rest period during electrode hook up, after which 3 minutes of eyes closed EEG was recorded. Participants sat upright in a comfortable chair in an

electrically shielded test chamber with head facing forward and eyes closed for three minutes during EEG recording, as timed by the researcher.

5.6.7. Electrophysiological recording

EEG was recorded from 8 scalp sites (F_Z, F_3, F_4, C_Z, C_3, C_4, P_Z, O_Z) via cap affixed with Ag^+/Ag^+Cl^- electrodes (EasyCap, Herrching-Brieibrunn, Germany) in accordance with the 10-20 system (Jasper, 1958). An additional electrode positioned between FP_Z and F_Z served as the ground, and a reference electrode was placed on the nose. Vertical (VEOG) electrooculographic activity was recorded via electrodes placed above and below the right eye, and horizontal (HEOG) activity was measured at the external canthus of both eyes. All sites showed an impedance below 5 kΩ during recording. EEG acvitiy was recorded using a Brain Vision amplifier and a Windows PC running Brain Vision Recorder software (Brain Products, Germany). Bandpass filters were set at 0.1-120 Hz and digitized continuously at 500 Hz.

5.6.8. EEG frequency band processing

A minimum of 45 artifact-free 2-s duration EEG epochs were subject to a Fast Fourier Transform algorithm, with high-pass autoregressive filter weighted by a 5% cosine taper for computation of average absolute power (μV^2). Frequency bands were defined according to Jobert and colleagues (2012) and included delta (1.5 - 6Hz); theta (6.0 - 8.5 Hz); $alpha_1$ (8.5 - 10.5 Hz); $alpha_2$ (10.5 - 12.5 Hz); alpha total (8.5 - 12.5 Hz); $beta_1$

(12.5 - 18.5 Hz); $beta_2$ (18.5 - 21.0 Hz) $beta_3$ (21.0 - 30.0 Hz) and gamma (30.0 - 40.0 Hz).

5.6.9. Statistical analysis

The Statistical Package for Social Sciences (SPSS, Chicago, IL) software was used to analyze natural logarithm transformed absolute power value changes induced by nicotine and moclobemide at 8 scalp regions. Analysis of each absolute power index involved a separate repeated measures analysis of variance (ANOVA) with drug condition (4 levels) and region (8 levels) as within-subject factors. Greenhouse–Geisser corrections were applied to all significant ($p < 0.05$) main and interaction effects, and Bonferonni correction was used in follow-up comparisons. To reduce the number of type I statistical errors, main effects of region were not followed up unless they interacted with drug condition.

5.7. Results

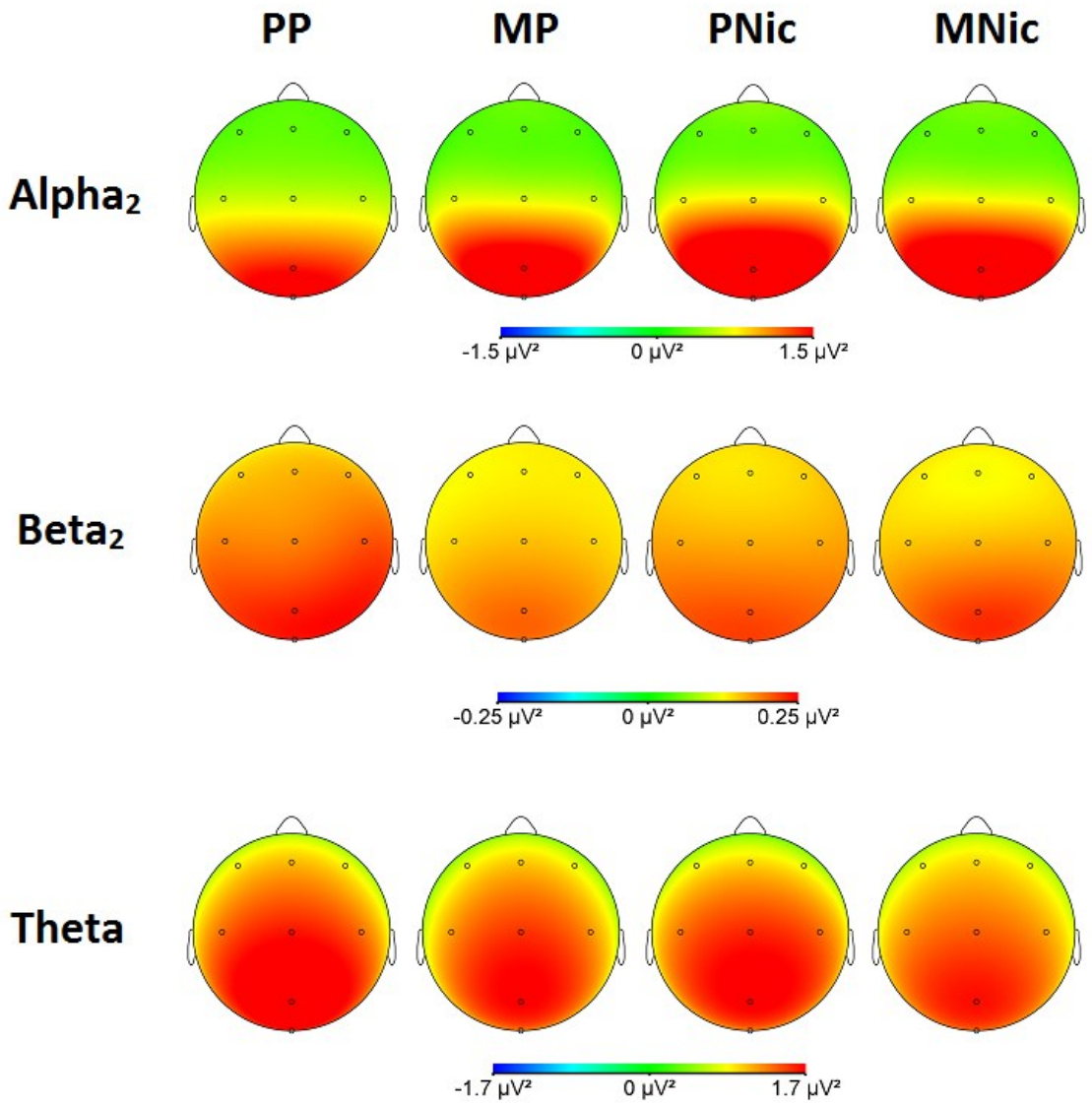

Figure 5.1: Topographic distributions of Alpha2 Beta2 and Theta band power for placebo/placebo (PP), moclobemide/placebo (MP), placebo/nicotine (PNic) and moclobemide nicotine (MNic) sessions.

There was a significant main effect of region ($p < .00$). Expected heterogenic topographic distributions of absolute power were observed in all frequency bands, with the exception

of Gamma, which did not reach significance (p = 0.90). Topographic distributions for bands in which a main drug effect was found are shown in Figure 5.1.

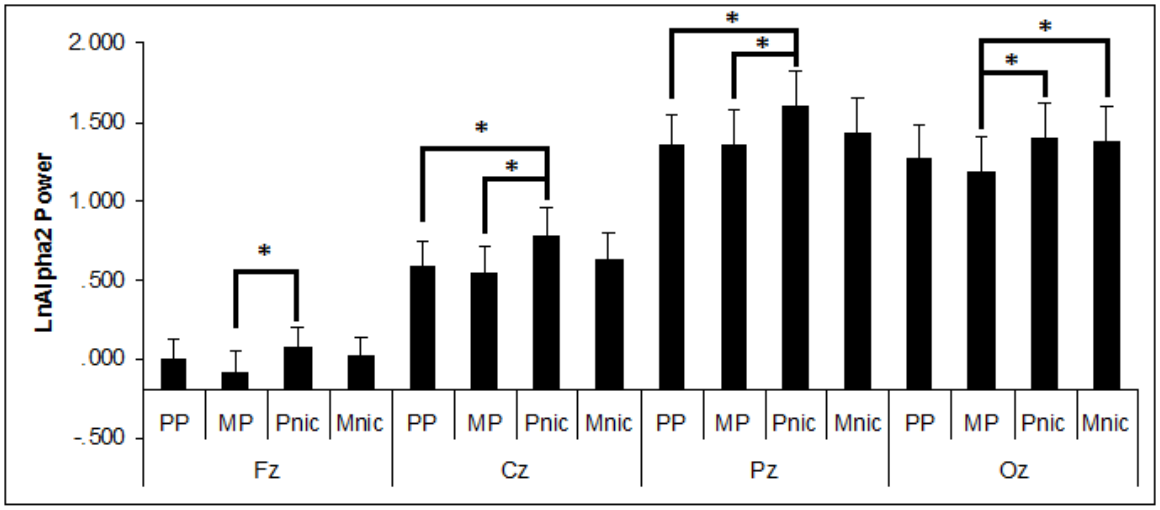

Figure 5.2: Mean LnAlpha2 power in 24 healthy subjects at midline sites (FZ, CZ, PZ, OZ) in four drug conditions: Placebo/Placebo (PP), Moclobemide/Placebo (MP), Placebo/Nicotine (PNic), and Moclobemide/Nicotine (MNic) . "*" indicates significance where p < .05. F or clarity, lateral sites (C_3, C_4, P_3, P_4) are not shown (see text for comparisons).

5.7.1. Alpha$_2$

Midline alpha$_2$ results are shown in Figure 5.2. A significant main effect of drug condition was found in the alpha$_2$ band F(2.75,63.33) = 3.77, p = .02. Follow up comparisons revealed overall higher alpha$_2$ power in the PNic condition (M = .649, SE = .16) compared to the MP condition (M = .450, SE = .16) p = .02.

Comparisons by site revealed PNic > MP differences were significant at F_Z (p < .00), F_3 (p < .00), F_4 (p < .00), C_Z (p < .00), C_3 (p < .05), C_4 (p < .00), P_Z (p < .03), and O_Z (p = .04). There was also a significant difference in alpha$_2$ power where MNic > MP at F_4 (p = .04), C_4 (p < .00), and O_Z (p = .04). Significant differences where PNic > PP were found

at C_Z ($p < .03$), C_4 ($p < .03$), and P_Z ($p = .04$). There was a trend for an effect where MP < MNic at F_Z ($p = .05$).

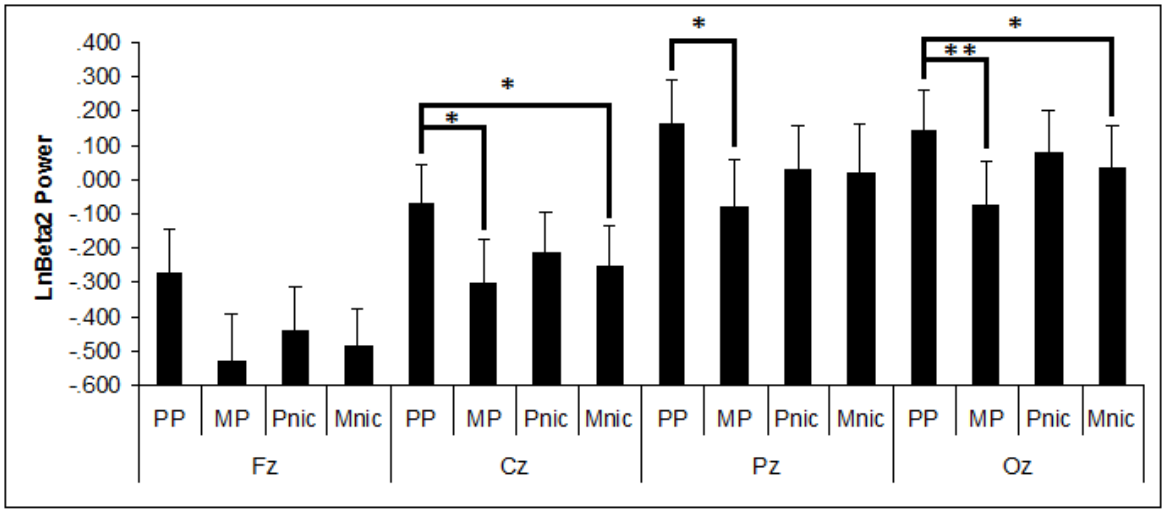

Figure 5.3: Mean LnBeta2 power in 24 healthy subjects at midline sites (FZ, CZ, PZ, OZ) in four drug conditions: Placebo/Placebo (PP), Moclobemide/Placebo (MP), Placebo/Nicotine (PNic), and Moclobemide/Nicotine (MNic) . "*" indicates significance where p < .05, "" indicates significance where $p < .01$. For clarity, lateral sites (C_3, C_4, P_3, P_4) are not shown (see text for comparisons).**

5.7.2. Beta$_2$

Midline Beta$_2$ results are shown in Figure 5.3. A significant main effect of drug condition was found in the beta$_2$ band $F(2.01, 46.28) = 3.31$, $p < .05$. Follow up comparisons revealed a significant difference where PP > MP at CZ ($p = .02$), C3 ($p = .03$), C4 ($p = .02$), PZ ($p = .02$), and OZ ($p = .00$). A significant difference where PP > MNic was found at CZ ($p < .05$). A significant difference where PP > PNic was found at C4 ($p = .03$). A significant difference where PNic > MP was found at OZ ($p = .02$).

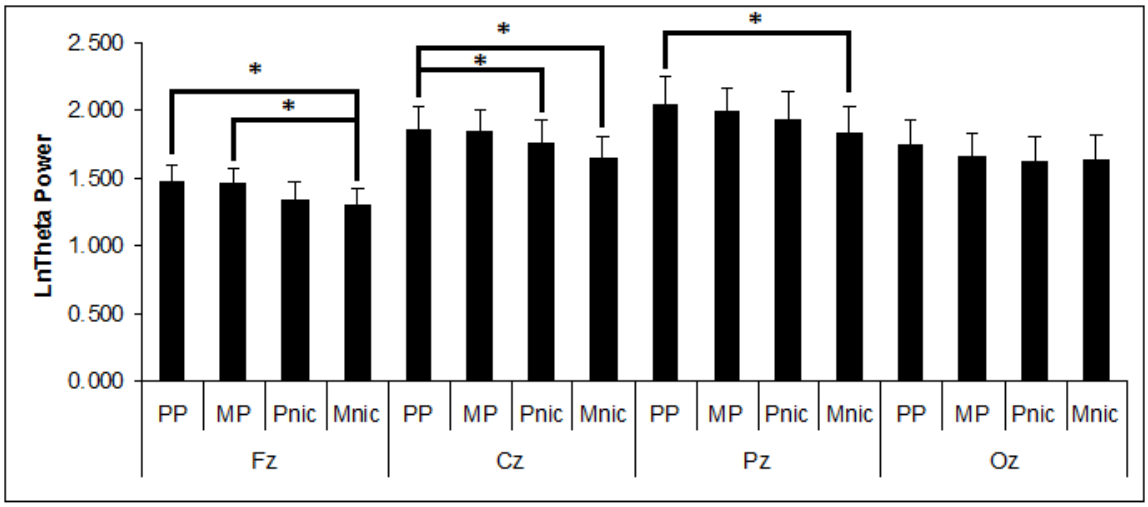

Figure 5.4: Mean LnTheta power in 24 healthy subjects at midline sites (FZ, CZ, PZ, OZ) in four drug conditions: Placebo/Placebo (PP), Moclobemide/Placebo (MP), Placebo/Nicotine (PNic), and Moclobemide/Nicotine (MNic) . "*" indicates significance where p < .05, "" indicates significance where *p* < .01. For clarity, lateral sites (C_3, C_4, P_3, P_4) are not shown (see text for comparisons).**

5.7.3. Theta

Midline theta results are shown in Figure 5.4. A significant main effect of drug condition was found in the theta band F(2.62, 60.26) = 3.08, p = .04. Follow up comparisons revealed higher overall theta power in the PP condition (M = 1.61, SE = .16) compared to the MNic condition (M = 1.44, SE = .15) p = .01.

Comparisons by site revealed significant differences where PP > MNic at F_Z (p = .01), F_3 (p < .04), F_4 (p < .01), C_Z (p = .00), C_3 (p = .00), C_4 (p = .00), and P_Z (p = .00). Significant differences were found where MP > MNic at F_Z (p = .01), C_4 (p = .02), C_Z (p = .01), C_3 (p = .04), and C_4 (p < .03).

5.7.4. Adverse events

There was a significant effect of drug F(1,23)=1.643, p = 0.033, due to higher severity ratings for symptoms in the PNic session (M=1.33, SE=0.00) compared to the PP session

(M=1.00, SE=0.00), p = 0.029 as well as compared to the MNic session (M=1.00, SE=0.00), p = 0.029.

5.8. Discussion

To our knowledge, this if the first study to examine the separate and combined effects of nicotine and MAO inhibition on resting EEG in healthy nonsmokers. The main findings of this study were increases of $alpha_2$ power by nicotine, a decrease of $beta_2$ power by moclobemide, and a decrease in both $beta_2$ and theta power by the combination of nicotine and moclobemide. Some significant site-specific effects reflected general trends in the overall topography, such as a decrease in $beta_2$ power by nicotine at C_4, and decrease of $beta_2$ power by the combination of nicotine and moclobemide at C_Z. While reports of adverse events were significant, mean symptom severity fell between "mild" and "none", and thus adverse symptoms such as nausea were likely not a confounding factor in drug EEG indexed drug differences.

The increase in $alpha_2$ power by nicotine is consistent with a previous study that examined acute nicotine in healthy nonsmokers (Fisher et al, 2012), which also found nicotine's effects to be specific to the $alpha_2$ band. The present study also showed nicotine-elicited decreases in the $beta_2$ band, which was not previously observed in nonsmokers, and is opposite to what was previously observed in abstaining smokers (Knott et al, 1999). Furthermore, both individual and combination administrations of nicotine and moclobemide decreased $beta_2$ power. Thus it seems that while $alpha_2$ oscillations are preferentially increased by nicotine, $beta_2$ oscillations are preferentially

decreased by moclobemide, and theta oscillations are preferentially decreased by the combination of both. While $alpha_2$ power was not significantly decreased by moclobemide, trends shown in Figure 5.1 and Figure 5.2 suggest differential influences of nicotine and MAO-A inhibition on $alpha_2$ and $beta_2$ power, with the combination condition resulting in an "averaging-out" of these effects. This observation may point towards a "cyclical" effect of smoking on brain states; that is, the chronic state of MAO inhibition in smokers could lead to a decrease in default mode network neuronal synchrony, and acute nicotine is sought to transiently alleviate this effect. One possible explanation is the upregulation of monoamines may diminish an established cortical signal to noise ratio (Hasselmo et al, 1997) whereas activation of nicotinic acetylcholine receptors may alleviate this effect (Winterer and Weinberger, 2004). Indeed, MAO-A inhibition has been shown to significantly exacerbate nicotine withdrawal symptoms in rats (Malin et al, 2013). A learned association between acute nicotine and temporary relief from MAO inhibition-related decreases in neural synchrony, possibly experienced as a lapse in cognition (Klimesch, 1999) may contribute to smoking addiction.

Conversely, the theta band showed smallest mean power in the nicotine/moclobemide combination condition, suggesting the two drugs reduce theta power in a synergistic manner. This decrease in theta is consistent with effects of cigarette smoking (Knott, 2001). Although increased theta has been associated with improved performance on declarative memory tasks, even when the subjects are unaware their memory will be tested (Klimesch et al,1996), a decrease in theta during the eyes closed resting state, such as in the current study, may reflect a functional decrease in theta band-associated cognitive load (Jensen and Tesche, 2002) in response to an environment with little

demand for encoding of memory. This nicotine/MAO-inhibition induced "lightening" of cognitive load through decreased hippocampal encoding at rest is a possible contributor to the mental state sought by smokers; evidenced anecdotally by the smoker who wishes to "clear the mind" by smoking after a difficult and/or stressful task.

The lack of a significant increase of theta power in the moclobemide condition compared to the placebo condition is inconsistent with a previous report showing increased theta associated with lower MAO activity (Hashimoto et al, 1988), however, the previous study did not differentiate between MAO-A and MAO-B activity, and thus it is possible that the two isoforms of MAO have differential effects on theta oscillations. Further study is required to examine the specific effects of MAO-B inhibition with and without nicotine on resting state EEG.

This study is limited to EEG measures; and as such we are unable to determine whether each subject shared similar levels of MAO-A inhibition, nor are we able establish the precise degree of nicotinic receptor activation/desensitization after nicotine gum chewing during EEG recording. A combination of MAO-A and MAO-B inhibition will be required in future studies in order to achieve a more accurate model of MAO inhibition in chronic smokers. While only males were used in the current study, results may differ between males and females as sex differences have been observed in nicotine response as well as monoamine systems in smokers and nonsmokers (Brown et al, 2012; Pogun et al, 2009; Fallon et al, 2005).

In summary, this study revealed that EEG-indexed $alpha_2$ and $beta_2$ neural oscillations are modulated differentially by nicotine and MAO-A inhibition, while theta oscillations are modulated by nicotine and MAO-A inhibition in a synergistic manner. MAO-A inhibition

in chronic tobacco users may differentially affect various neural and cognitive processes, and thus MAO inhibition should be considered as an important factor in the treatment of tobacco addiction.

CHAPTER 6

General Discussion

6.1. Summary of Findings

The purpose of this thesis was to elucidate the effects of nicotine and MAO-A inhibition on early auditory cognitive processes known to be altered in both chronic smoking and schizophrenia. Drug conditions consisted of placebo (PP), nicotine (PNic), moclobemide (MP), and a combination of nicotine and moclobemide (MNic). Cognition was measured in the form of P50 paired-stimulus, optimal-5-MMN, and P300 (P3a & P3b) ERP paradigms, as well as 3 minutes of eyes-closed resting-state EEG recording. Participants consisted of 24 healthy nonsmoking males, and data was analyzed both using the total sample (N = 24), as well as low and high baseline cognition groups (N = 12 each) using placebo-session ERPs in each paradigm as the basis for a median split. The main findings of this report are summarized below.

In the total (N = 24) group, significant effects of drug condition were observed in the P50 paradigm, as well as the P300 paradigm and in the $alpha_2$, $beta_2$, and theta EEG frequency bands. No significant total-group drug effects were observed in the MMN paradigm. Compared to placebo, the combination MNic condition improved P50 gating, and also reduced theta activity consistently along midline scalp sites. The MNic condition also reduced $beta_2$ power compared to placebo, but the effect was less robust than in the MP condition. The MNic condition did not significantly alter either MMN or P300 measures compared to placebo. The PNic condition significantly increased P3b amplitude and $alpha_2$ power compared to placebo, as well as $alpha_2$ power. The MP condition increased P3a amplitude compared to placebo, and reduced $beta_2$ power.

Differential paradigm-dependant effects were also observed in the low-baseline cognition groups (N = 12). Improved P50 gating was found in the MNic condition compared to placebo. The PNic condition increased duration MMN amplitudes as well as P3b amplitudes compared to placebo. The MP condition increased duration and location MMN amplitudes, as well as both P3a and P3b amplitudes, compared to placebo.

In high-baseline cognition groups (N = 12), the MNic condition decreased gap and location MMN amplitudes, compared to placebo. The PNic condition decreased P50 gating, as well as gap and intensity MMN amplitudes, compared to placebo. The MP condition decreased gap MMN amplitudes compared to placebo.

6.2. Interpretation of results

6.2.1. Moclobemide

The main effect of moclobemide in the absence of nicotine was an increase in involuntary attention, indexed by P3a amplitude in response to novel stimuli, as well as a decrease in $beta_2$ power, in the total sample (N=24). The specificity of moclobemide to the P3a may result from the effect of MAO-A inhibition on DA release, i.e. an increase in vesicular capacity and thus higher amounts of neurotransmitter release upon activation of VTA neurons. P3a generation is theorized to rely strongly on dopaminergic activity (Polich, 2007). Furthermore, it has been proposed that DA neurons respond to salient, non-reward events (Horvitz, 2000) including novel stimuli (Rebec, 1998), supporting DA as a modulator of P3a. In a genetic study, the Met/Met variant of the COMT polymorphism

was associated with decreased DA metabolism, and carriers of this allele exhibited enhanced P3a amplitudes in the frontal region (Heitland et al, 2013). The increase in P3a amplitude following MAO-A inhibition in this thesis may have resulted from a similar mechanism. While beta power has been associated with attentional effort during cognitive tasks (Stoll et al, 2015), a moclobemide induced decrease in beta power might reflect an attentional shift away from the task, or, in other words, a decrease in inhibition of task-irrelevant stimuli, such as the novel, distracting tones which elicit the P3a.

In low-cognition groups, moclobemide also increased MMN amplitude to duration and location deviants, as well as both P3a and P3b amplitudes. A MAO-induced increase in NA release likely contributed to the increase in P3b amplitude, as P3b has been associated with parietal NA pathways (Polich, 2007). It is also possible that some degree of DA-dependent salience detection also applies to both the MMN and P3b paradigms, and that in low-baseline individuals, the contribution of increased DA is magnified, resulting in a significant difference compared to placebo. The increase in MMN duration deviants was particularly surprising; although DA and 5-HT modulation has been shown to have no effect on MMN amplitude (Leung et al, 2007), it is possible that increased neurotransmitter release, such as via MAO-inhibition, can improve MMN, but only in individuals with low baseline amplitudes, a factor that was not investigated previous studies. DA modulation via antipsychotics have not consistently shown improvement of MMN amplitudes in SZ patients (Korostenskaja et al, 2005), suggesting that diminished MMN amplitudes in low-baseline individuals in the current thesis do not result from the same mechanism as in SZ, where an NMDA dysfunction is theorized to play a central role (Javitt, 2000).

6.2.2. Nicotine

The main effect of nicotine in the absence of moclobemide was an increase in auditory target processing, indexed by P3b amplitude, as well as an increase in alpha$_2$ power, in the total sample (N=24). The improvement of the attention-dependent P3b via nicotine likely reflects an activation of cholinergic mechanisms involved in task-related stimulus detection (Sarter, Givens, and Bruno, 2001), such as nAChR rich areas in the thalamus and PFC. The thalamo-cortico pathway may have been particularly important in our P300 paradigm, in which target tones were distinguished from standard tones solely by frequency differences, and thus no "top down" pattern detection heuristics were useful in their identification, supporting the "bottom up" theory of cholinergic-dependant cognition. Although alpha frequency EEG has been associated with top-down processing (Cooper et al, 2003), it has been suggested that increased cortical alpha might actually reflect an inhibition of non-essential cognitive processes in favour of the task at hand (Bazanova and Vernon, 2014), consistent with the increase in P3b, but not P3a amplitudes observed in the current thesis. While nicotine has been previously shown to have no effect on P3b (Evans et al, 2014), this recent study utilized self-report measures of cognitive control in order to stratify participants as high-or-low cognition, instead of using baseline P3b amplitude as was done in the current study. Therefore, it is possible that the self-report measures of cognitive control did not accurately reflect the efficiency of cholinergic-dependant target-detection in the previous study. Our current results are more in line with previously observed inverted-U effects of nicotinic activation (Knott et

al, 2015), and this was also reflected in the MMN paradigm, with nicotine improving duration deviant amplitudes in low baseline individuals, and reducing intensity and gap amplitudes in high baseline individuals. Moreover, nicotine also reduced P50 gating in high baseline performers. Therefore, it seems that nicotine's actions on cognition are consistently baseline-dependant, with inverted-U effects observed across multiple cognitive processes.

6.2.3. Moclobemide/Nicotine combination

The main effects of the MNic condition were improvements in P50 sensory gating, as well as a decrease in theta power. These findings are supported by an animal study that found increased hippocampal theta power decreased sensory gating in rats (Schridde and van Luijtelaar, 2001). Although, caution should be used when comparing hippocampal theta to scalp-recorded EEG theta frequencies, these two different phenomena may be related in reflecting hippocampus-dependent cortical activity (Klimesch et al, 1996). It is tempting to interpret improvement in P50 gating during the MNic condition to i) an increase in DA release potential due to MAO-A inhibition and ii) an increase in DA neuron activity due to nicotine's actions on VTA neurons. However, DA increase has been shown to reduce, rather than improve P50 gating (Light et al, 1999), and furthermore, the fact that the MNic condition did not also show an increase in the DA-dependant P3a component suggests that the MNic conditions' improvement of P50 gating relative to baseline involves more than DA modulation alone. It has been proposed that optimal sensory gating depends on proper functioning of inhibitory hippocampal

microcircuits, and that both dopamine modulation of neuronal signal-to-noise, and cholinergic potentiation of inhibitory interneurons are necessary for this to occur (Moxon, Gerhardt, and Adler, 2003). In this model, the inverted-U actions of both the cholinergic and dopaminergic system are at play; an increase in DA beyond optimal levels on the response curve leads to an increased neuronal "gain" (Lodge and Grace, 2011), i.e. a state in which a lack of inhibition leads to hyperactivity in hippocampal pyramidal cells. This in turn necessitates increased cholinergic activation of GABAergic feedback inhibition in order to return the system back to optimal functioning. Thus, while the P3a is most sensitive to an increase in dopaminergic tone, and while the P3b is most sensitive to cholinergic induced focus of attention through activation of inhibitory interneurons, the gating of the P50 ERP is sensitive to a balance of both systems. This phenomenon is readily apparent in our subgroups. Low baseline gating individuals showed significantly improved gating only in the combination MNic condition, but the high baseline gating subgroup showed optimal gating in both the placebo condition as well as the combination MNic condition. Thus, in optimally-gating individuals, a challenge to either nAChR or DA dependent mechanisms results in diminished gating efficacy, whereas simultaneous activation of both mechanisms results in a return to optimal performance, presumably by re-balancing these two systems in key brain areas such as the hippocampus.

6.2.4. Implications for SZ

The hippocampal microcircuits responsible for sensory gating discussed above have been implicated in recent theories of SZ, where dysfunction of NMDA receptors and

GABAergic inhibitory interneurons are theorized to cause hippocampal hyperactivity, resulting in disinhibition of VTA DA neurons (Perez and Lodge, 2014). Therefore, as the acute effects of nicotine diminish after smoking, an increase in synaptic DA facilitated via MAO-inhibition may exacerbate SZ symptoms associated with DA-induced hyperactivity. Combined with the fact that SZ patients tend to be extremely heavy smokers, these findings suggest that the cognitive impact of smoking withdrawal in patients may be severe. Therefore, the results of this study strongly support a treatment program for SZ patients which encourages smoking cessation, with the caveat that patients may require pharmacological intervention, such as MAO-inhibitors, in order to suppress a potential increase in cognitive symptoms.

Simple sensory paradigms such as those used in this thesis are well suited to SZ research, because the molecular mechanisms involved in these early auditory processing steps are shared with other higher order processing circuits throughout the brain. Thus, amelioration of early auditory cognition could have a downstream therapeutic effect on more abstract symptoms such as hallucinations and delusions. As such, the observations in the current thesis; that different ERP paradigms showed different sensitivities to each drug condition, suggests that neither cholinergic activation nor monoamine modulation are likely to be effective at treating every facet of SZ. A large, multi-faceted cognitive battery (such as MATRICS) should therefore be used when testing the efficacy of novel SZ treatments, and, by identifying the degree of deficit/improvement in each cognitive domain, this strategy could allow for targetting of mechanism-specific dysfunctions on a patient by patient basis. In fact, given the links between nicotine, monoamines, and the different aspects of cognition observed in this thesis, the smoking habits of indivdual SZ

patients may themselves be clues to the neuromolecular factors underlying their specific symptoms, and may provide insight into which treatment strategies will be most effective.

6.2.5. Implications for tobacco addiction: cognition as a "moving target"

If, as studies suggest, smokers use tobacco not just for an immediate, pleasurable sensation, but also to achieve a desired state of mind, i.e. enhanced cognition, then the results of the current thesis may aid in explaining smoking's high addiction potential. Three mechanisms are at play: the time course of nicotine-induced activation/desensitization of nAChRs (hours, with sharp decline after 10 minutes; Domino, 1998), the onset of MAO inhibition via commencement of smoking (unknown; Fowler et al, 1999) which continues after cessation (weeks; Berlin, 2001), and finally, the upregulation of MAO enzyme synthesis in chronic smokers (years, Rendu, 2011). Smokers may unwittingly and unknowingly find themselves in a position wherein they are constantly searching for a balance between the relatively short-acting cholinergic and dopaminergic effects of nicotine, and the longer-lasting neurotransmitter-modulating effects of MAO inhibition. After smoking, as the effects of nicotine fade and MAO-inhibition-induced increases in monoamine levels remain, cognition may decrease below baseline, due to a mismatch of each system on their respective inverted-U curves. As users cannot "unsmoke", the only available remedy to this conundrum is to light another cigarette, in order to titrate their intake for optimal effects, with increased use leading to increased dopaminergic reinforcement, ultimately leading to an increase in smoking rate.

Furthermore, because different aspects of cognition were shown to be differentially sensitive to nicotine, MAO-inhibition, and the combination of both, the supposed "optimal level" of smoking-induced brain activation is likely dependant on an individual's internal and external environment, including cognitive load and task demands. Thus, optimal cognition in smokers can be described as a "moving target"; the pursuit of which may succeed for short, fleeting moments, but for the most part, remains constantly unfulfilled. The end result of this cycle is chronic smoking, and the well known, often fatal health consequences associated with tobacco use. For this reason, smoking cessation therapies should take both nAChRs and monoamine neurotransmitters into account, as both mechanisms likely contribute to withdrawal.

6.2.6. Strengths, Limitations and Future Directions

The studies contained in this thesis were the first to experimentally investigate the separate and combined effects of nicotine and MAO inhibition on early cognitive ERPs. Being the first of their kind, these studies were designed to avoid any confounding effects of tobacco addiction, withdrawal, and clinical status, by using nonsmoking healthy controls in a randomized, double-blind, placebo-controlled crossover design, with counterbalanced drug conditions used in repeated measures. Moclobemide was used to selectively and reversibly inhibit MAO-A, however, because smokers exhibit an inhibition of both MAO-A and MAO-B, the logical next-step for future studies will be to utilize a selective MAO-B inhibitor, such as safinamide, as well as a nonselective

inhibitor, such as ladostigil, in order to assess the specific contribution of each isoform to cognition in isolation and when paired with nicotine.

Future studies may also benefit from comparing healthy controls to a group of abstaining smokers in order to assess cognitive effects of these drugs during nicotine withdrawal. This approach presents challenges however, since the lasting effects of tobacco smoke-induced MAO inhibition are unclear. For example, PET imaging found withdrawal-induced increases in MAO-A activity in the prefrontal cortex of heavy smokers during withdrawal, but this effect was not found in moderate smokers (Bacher et al, 2011). Furthermore, MAO activity in these heavy smokers after 8 hours of withdrawal was higher than MAO activity in healthy nonsmoking controls; an effect which may result from upregulation of MAO enzyme synthesis during inhibition (Rednu et al, 2011). Therefore, pharmacologically inhibiting MAO during withdrawal from heavy smoking may actually return MAO activity to levels comparable to those in healthy controls. Therefore, studies of cognition in tobacco smokers should be very carefully controlled to avoid potentially confounding effects of differential MAO activity in individuals of varying smoking rates.

Although inverted-U type effects on cognition have repeatedly been shown following both cholinergic activation and DA modulation, a major limitation of this thesis is the use of median split to classify individuals as "low" or "high" cognition. All participants were screened for current, past, or family psychopathology, and thus our use of "low cognition individuals" serves less as a model of psychiatric disease, and more of a "proof of concept" demonstration, designed to show that specific aspects of cognition can be modulated by nicotine and/or moclobemide. Modelling psychopathology in healthy

humans is challenging, however, one promising strategy involves the use of NMDA antagonists, such as ketamine, in order to transiently induce SZ-like symptoms in healthy controls. Recent studies have shown ketamine to induce cognitive deficits much like those observed in SZ, and there is some evidence that nicotine can rescue at least some portion of these deficits (Knott et al, 2012), and future studies may benefit from also investigating the effects of MAO inhibition under these conditions.

6.2.7. Conclusion

Overall this thesis demonstrates differential effects of nicotine and MAO-A inhibition on cognition. The main findings include a synergistic improvement by nicotine and moclobemide of P50 sensory gating associated with theta power reduction, a nicotine-sensitive improvement of the P3b associated with $alpha_2$ power increase, and a moclobemide-sensitive improvement of the novelty P3a associated with $beta_2$ power decrease. In subgroups of baseline cognition, evidence of an inverted-U effect on cognition was seen in all paradigms, including the duration MMN deviant, which was previously thought to be unmodulated by monoamine neurotransmitters. Therefore, this thesis provides indirect evidence that different components of tobacco smoke have differential and/or synergistic effects on cognition, depending on the task or paradigm, as well as on baseline cognition. Going forward, studies which focus on the cholinergic and monoaminergic basis of cognition in smoking, as well as in schizophrenia, should take these findings into account. It is hoped that an increased understanding of both nicotine and MAO-inhibition will ultimately lead to more effective smoking cessation treatments,

improved schizophrenia medications, as well as a better overall understanding of cognition in humans.

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