Monoamine Oxidase and Sensory Gating:
Psychophysiological Vulnerabilities among Teenage Smokers

by

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(ABSTRACT)  

Smoking is one of the leading causes of death in the world. About 80% of smokers start smoking before the age of 18. In the Appalachian area and the South in the United States, smoking percentages among adults and adolescents are higher than in other regions. Female smoking shows a variety of different trends from male smoking, and smoking brings particular health problems related to production to female smokers. These findings highlighted the importance of studying female teenage smokers in southwest Virginia. The initial project aimed to identify risk factors that might prevent smoking in an early stage. Dr. Helen Crawford led the Cognitive Neuroscience Lab at Virginia Tech in discovering the psychophysiological vulnerabilities of female teenage smokers. Toward this end, event-related potential (ERP), personality, and behavioral data were collected in teenage female smokers and non-smokers. These data were analyzed to examine possible psychophysiological vulnerabilities in female teenage smokers such as deficits in brain and cognitive function, personality traits, and environment influences (Crawford, Justin, & Wan, 2004). The purpose of this dissertation is to further analyze these data to elaborate and clarify the relationships among these vulnerabilities toward understanding teenage smoking behavior.

Participants were 49 teenage girls (smokers and non-smokers) with age from
14 to 18. The measures included sensory gating, platelet MAO-B activity, attention, memory, temperament, schizotypal personality, recognition of facial expressions, taste and smell. The initial set of analyses compared smokers and non-smokers, including those classified as high and low dependent, on all dependent measures. The results suggested some psychophysiological vulnerabilities in female teenage smokers, which have been used as support for the self-medication and the orbito-frontal dysfunction models of why teenagers smoke (Crawford et al., 2004). Further examination of these factors may help teenagers to reduce the smoking dependency and possibly improve cognitive function.

Specifically, this dissertation focused on the role of the variable of monoamine oxidase-B (MAO-B) in the correlations among sensory gating, MAO and other cognitive and personality measures. All smokers were divided into high and low MAO groups first. Comparison analyses were conducted between them. The high MAO group showed better sensory gating function than the low MAO group. Correlation analyses were conducted among all of the measures. The significant linear relationships between MAO and sensory gating, MAO and CO level and MAO and temperament were demonstrated. MAO activity positively correlated with the sensory gating function and negatively correlated with CO level and temperament characteristics. Finally, to explore the mechanisms of the relationship between MAO and sensory gating, the neurotransmitter systems related to MAO and sensory gating were discussed.
Dedication

First of all, I would like to thank my committees: Dr. Bruce H. Friedman, for his serving as the chairperson and his assistance and guidance for the Ph.D study plan and the whole dissertation work; Dr. David Harrison and Dr. Martha Ann Bell, for their valuable suggestions for the dissertation work and consistent support throughout all my work and study in Virginia Tech; Dr. Neal Jr. Castagnoli and Mrs. Kay Castagnoli in the Department of Chemistry, for their participation and providing guidance and suggestions with their profuse experiences.

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Chapter 1

Introduction: Initial Project Description and Literature Review

This dissertation is about one part of the project “Psychosocial Risk Factors and Prevention Strategies for Adolescent Female Smokers in Virginia”, which was conducted in the Cognitive Neuroscience Lab in Virginia Tech. It will present the project design, background information, data collection, data analyses, results, and discussion. Specifically, it will focus on monoamine oxidase and sensory gating and discuss the neurotransmitters related to them.

1. Initial Project Description

“Psychosocial Risk Factors and Prevention Strategies for Adolescent Female Smokers in Virginia” was an interdisciplinary research project conducted among the Departments of Human Development, Psychology and Chemistry at Virginia Tech from 2002. There were multiple aims of this project, including: (a) to collect and analyze data on Virginia female teenagers’ smoking behavior; (b) to identify the risk and protective factors influencing this smoking behavior; (c) to identify effective program intervention, and (d) to assess the role of the relationship between sensory gating and frontal lobe functioning with smoking (Meszaros, 2004).

The relevance of such research is clear. Smoking is one of the leading preventable causes of death in the world. Per year, there are nearly 50 million Americans who smoke. However, 80% of these individuals have been found to start smoking before the age of 18 (U.S. Department of Health and Human Services, 1994). One-third of American people who start smoking before the age of 17 will die because of smoking related diseases.
According to a recent Center for Disease Control (CDC) Morbidity and Mortality Weekly Report (2004), current, regular cigarette usage among teenagers increased into the late 1990s, but had declined significantly by 2003. Yet, a substantial number of teenagers still smoke: in 2003, 21.9% of girls and 21.8% of boys in high school reported current cigarette use in the United States. Moreover, studies have found that in the Appalachian area and the South, including Virginia, Alabama, Kentucky, North Carolina, Tennessee, and West Virginia, smoking percentages among adults and adolescents are higher than in other regions in the United States. For example, 43.7% of West Virginia females are current cigarette smokers (CDC, 1999).

Female smoking shows a variety of different trends from male smoking. The number of female smokers has increased steadily while the number of male smokers decreased from the mid-1980s to the mid-1990s (CDC, 1999). Female smokers are at high risk for reproductive disorders and pregnancy problems (Berman & Gritz, 1991). Female smokers who take oral contraceptives have a higher risk of stroke, spontaneous abortion, bleeding during pregnancy, perinatal mortality, stillbirth, preterm delivery, and low birth weight babies (National Center on Addiction and Substance Abuse, 2003). Therefore, smoking brings particular problems to female smokers related to reproductive health.

These findings highlighted the importance of studying female teenage smokers in southwest Virginia. The initial project aimed to identify risk factors that might prevent smoking in an early stage. Dr. Helen Crawford led the Cognitive Neuroscience Lab at Virginia Tech in discovering the psychophysiological vulnerabilities of female teenage smokers. Toward this end, event-related potential (ERP), personality, and behavioral
data were collected in teenage female smokers and non-smokers. These data were analyzed to examine possible psychophysiological vulnerabilities in female teenage smokers such as deficits in brain and cognitive function, personality traits, and environment influences (Crawford, Justin, & Wan, 2004). The purpose of this dissertation is to further analyze these data to elaborate and clarify the relationships among these vulnerabilities toward understanding teenage smoking behavior.

Participants were 49 teenage girls (smokers and non-smokers) with age from 14 to 18. The measures included sensory gating, platelet MAO-B activity, attention, memory, temperament, schizotypal personality, recognition of facial expressions, taste and smell. The initial set of analyses compared smokers and non-smokers, including those classified as high and low dependent, on all dependent measures. The results suggested some psychophysiological vulnerabilities in female teenage smokers, which have been used as support for the self-medication and the orbito-frontal dysfunction models of why teenagers smoke (Crawford et al., 2004). Further examination of these factors may help teenagers to reduce smoking dependency and possibly improve cognitive function.

Specifically, this dissertation focused on the role of the variable of platelet monoamine oxidase-B (MAO-B) activity in the correlations among sensory gating, MAO activity and other cognitive and personality measures. All smokers were divided into high and low MAO groups first. Comparison analyses were conducted between them. The high MAO group showed better sensory gating function than the low MAO group. Correlation analyses were conducted among all of the measures. The significant linear relationships between MAO and sensory gating, MAO and CO level and MAO and
temperament were demonstrated. MAO activity positively correlated with the sensory gating function and negatively correlated with CO level and temperament characteristics. Finally, to explore the mechanisms of the relationship between MAO and sensory gating, the neurotransmitter systems related to MAO and sensory gating were discussed.

2. Literature Review

Two theoretical models of smoking, drawn from prior research, are relevant to the present study (Crawford, McClain-Furmanski, Castagnoli, & Castagnoli, 2002). These models, the self-medication model and the orbitofrontal/disinhibition model, are briefly described below.

2.1. Self-medication Model

Smoking has been considered as self-medication for psychiatric patients (Menza, Grossman, Van Horn, Cody, & Forman, 1991; Hall, Munoz, & Reus, 1994). Studies have found that tobacco use and/or dependence is associated with several psychiatric conditions including depression, bipolar disorder, problem gambling, antisocial personality disorder, schizophrenia, and borderline and schizotypal personality traits (Dinn, Aycicegi, & Harris, 2004; Hughes, Hatsukami, Mitchell, & Dahlgren, 1986). Smoking may help individuals with schizophrenia reduce negative symptoms and enhance cognitive function (Dalack, Healy, & Meador-Woodruff, 1998; Taiminen et al., 1998; Lyon, 1999). Nicotine patch administration in abstaining schizophrenics can improve working memory, as assessed by the N-back paradigm (e.g., Jacobsen et al., 2004). Smoking deprivation impaired cognitive performance and re-administering cigarettes enhanced this performance in healthy smokers (Bell, Taylor, Singleton,
Henningfield, & Heishman 1999; Heishman & Henningfield, 2000; Sakurai & Kanazawa, 2002). Smokers also showed significantly more schizotypal traits than non-smokers on these measures in some studies (Larrison, Briand, & Sereno, 1999; Kolliakou & Joseph, 2000; Alvarez-Lopez, Gutierrez-Maldonado, & Andres-Pueyo, 2001).

Studies on attention-deficit/hyperactivity disorder (ADHD) have found that the rate of smokers among ADHD individuals was significantly higher than the general population for both adults and adolescents (Masterson, & O’Shea, 1984; Ziedonis, Kosten, Glazer, & Frances, 1994). Specifically, inattention symptoms and related deficits in executive functioning significantly predict smoking (Menza et al., 1991; Sandyk, 1993; Kelly & McCreadie, 1999; Riutort, Cuervo, Danion, Peretti, & Salame, 2003). Studies have generally found that smoking enhances cognitive function, especially attentional function among individuals with ADHD (Pomerleau, Downey, Stelson, & Pomerleau, 1995; Coger, Moe, & Serafinides, 1996; Levin et al., 1996; Conners et al., 1996).

The above findings suggest that the augmenting effects of smoking on attention and executive functioning may increase its usage among patients with schizophrenia and ADHD, because smoking helps diminish the cognitive dysfunctions among these patients. Smoking in adolescents may also be a form of self-medication or mood regulation (see Dinn et al., 2004). According to this self-medication model, teenage smokers might have some cognitive deficits originally and they use smoking to enhance cognitive function. For this reason, comparisons of sensory gating, attention, and memory among teenage smokers and non-smokers might help identify the cognitive vulnerabilities among teenage smokers.
2.2. Orbitofrontal/disinhibition Model

The self-medication model explains why some people smoke; the orbitofrontal/disinhibition model will explain these motives in terms of the effects of smoking on the brain. This model suggests that the orbitofrontal cortex is an important brain structure which contributes to drug addiction (Volkow & Fowler, 2000). The initial drug self-administration activates reward circuits in the brain such as the nucleus accumbens and amygdala. Continued drug use leads to intermittent dopaminergic activation which in turn promotes orbitofrontal dysfunction via the striato-thalamo-orbitofrontal circuit. Numerous studies have found a link between smoking and orbitofrontal function. For example, smokers show cognitive deficits in go/no-go, antisaccades, delayed alternation, and impulsivity rating tests, which are related to orbitofrontal activity (see Spinella, 2002). Additionally, some studies have found that recognition of facial expressions, emotion, smells and odors are associated with orbitofrontal activity (LeDoux, 1993; Rolls & Baylis, 1994; Rolls, Critchley, Browning, & Hernadi, 1998). With the perception test of phenylthiocarbamide (PTC), smokers report no PTC taste more frequently than non-smokers (Enoch, Harris, & Goldman, 2001). Studies have also found olfactory deficit (Moberg et al., 2003) and impaired recognition of facial expressions (Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004) in schizophrenia. Because many individuals with schizophrenia smoke, we do not know whether these deficits resulted from smoking or from schizophrenic disorder. To explore how smoking affects the function of the orbitofrontal cortex among
teenage smokers, the recognition of facial expressions, smell, and taste were measured in this project.

2.3. The Effect of Smoking on Human Sensory Gating

_Sensory gating_ is a term used to describe the brain’s filtering function, which helps to prevent incoming irrelevant sensory information from entering the higher cortex and ensures normal information processing (Braff & Geyer, 1990). Successful sensory gating is therefore an important property of the normal functioning brain. Deficits in sensory gating can result in an overflow of irrelevant stimuli, which has been associated with behavioral disorders and psychotic symptoms (McGhie & Chapman, 1961), and can lead to sensory overload and cognitive fragmentation (Croft et al., 2001).

Usually, sensory gating is measured with the conditioning-testing P50 paradigm (Adler et al., 1982; Freedman, Adler, Waldo, Pachtman, & Franks, 1983). This procedure examines suppression of the cortical response to a second (S2 or test) stimulus delivered after an identical first (S1 or conditioning) stimulus, presented in pairs (stimulus onset asynchrony interval = 500 ms), with an interval of 8-10 sec between pairs. Sensory gating can be measured by the ratio of the P50 amplitudes of S2 and S1, by the difference between them, or by the ratio of P50 – N40 of S2 and S1. Low ratio or large differences represent better sensory gating (Freedman et al., 1983). Control participants can typically reduce the amplitude of S2 by 80-90% of the amplitude of S1, but schizophrenics only reduce this amplitude by 10-20% (Freedman et al., 1983).

Sensory gating has been shown to have a positive relationship with the performance in attention test (Wan, Crawford, Boutros, & Friedman, in preparation). The prefrontal
cortex has been suggested to play an important role in sensory gating and attention. For example, the prefrontal-thalamic inhibitory system was found to suppress irrelevant inputs and select relevant ones at an early stage of sensory processing (Edinger, Siegel, & Troiano, 1975; Alexander, Newman, & Symmes, 1976; Skinner & Yingling, 1977). Damage to the prefrontal cortex disrupts inhibitory modulation of sensory inputs to primary sensory cortex (Knight, Scabini, & Woods, 1989, Yamaguchi & Knight, 1990). Patients with prefrontal lesions are less able to filter out irrelevant sensory inputs and cannot sustain attention (Knight, Staines, Swick, & Chao, 1999). Patients with prefrontal cortex lesions have shown poor concentration and organization and were more vulnerable to disruption from proactive interference (Thompson-Schill et al., 2002). Prefrontal cortex lesions in the human are associated with the ability to sustain attention, particularly over a long delay (Wilkins, Shallice, & McCarthy, 1987), as well as with diminished divided attention (Godefroy, Lhullier, & Rousseaux, 1996) and reduced ability to shift attentional set (Manes et al., 2002). Animal studies have shown similar results in monkeys (Dias & Segraves, 1996) and rats (Muir, Everitt, & Robbins, 1996).

Previous studies have found that smoking normalizes sensory gating deficits in schizophrenia (Adler, Hoffer, Wise, & Freedman, 1993; Griffith et al., 1998), smokers show better sensory gating than non-smokers among healthy people (Crawford et al., 2002), and that smoking and schizotypal personality are mediating factors of sensory gating (Wan, Crawford, & Boutros, in press). Based on these findings, sensory gating, attention, and schizotypy measures were used in the present study.

2.4. The Effect of Smoking on Human MAO Activity
Monoamine oxidase (MAO) activity is another important index of the effect of smoking on the brain. MAO catalyzes the oxidative deamination of exogenous amines in the brain and peripheral tissues (Johnston, 1968; Knoll & Magyar, 1972). Cigarette smoking has inhibiting property on platelet MAO-B activity (Yu & Boulton, 1987; Norman, Chamberlain, & French, 1987; Berlin et al., 1995). Oreland, Fowler, & Schalling (1981) reported decreases of 14% (using tyramine as the substrate) and 22% (using β-phenylethylamine as the substrate) in platelet MAO-B activity in female smokers compared to non-smokers. A 15% decrease in platelet MAO-B activity among regular smokers compared with ex-smokers, non-smokers or occasional smokers has also been found (Norman, Chamberlain, French, & Burrows, 1982; von Knorring & Oreland, 1985). Brain imaging studies have shown a similar inhibiting effect of smoking on brain MAO levels (Fowler et al., 1996a, b). Specifically, smoking reduced brain MAO-A by 28% and MAO-B by 40%.

Studies have also found that low platelet MAO is associated with increased impulsivity and inattention in boys with ADHD (e.g. Shekim et al., 1986). Changes in platelet MAO-B activity were associated with attention deficits in adolescents (Kiive, Merenakk, Harro, & Harro, 2005). A genetic study also linked the 941G/T MAO-A polymorphism (but not the MAO-B gene) and ADHD development in an Irish sample (Domschke et al., 2005).

Studies have also found relationships among platelet MAO activity, personality, and temperament (Buchsbaum, Coursey, & Murphy, 1976; Schalling, Asberg, Edman, & Oreland, 1987). People with lower MAO-B activity levels (with unknown smoking status)
were found more vulnerable to certain psychiatric disorders such as schizophrenia and bipolar disorder, and showed a greater tendency toward alcoholism, psychopathy, and attempted suicide (Buchsbaum et al., 1976; Baron, Levitt, Gruen, Kane, & Asnis, 1984).

High MAO-B individuals tended to show less sensation seeking and conformity but more psychasthenia, muscular tension and suspicion than low MAO-B individuals (Schalling et al., 1987).

Based on the above findings, platelet MAO-B activity, schizotypy and temperament were measured in the initial study among teenagers in relation to their smoking status. In this dissertation, MAO-B activity is examined in relation to these variables, as well as with sensory gating and attentional performance.
Chapter 2

Data Collection and Processing

1. Subject Recruitment and Inclusion/Exclusion Criteria

Smoking and non-smoking teenage girls were recruited for the initial study. Inclusion criteria were: (1) female between the ages of 14 to 18 years; (2) in a general state of good physical and mental health as reported by a parent, with no known medical or neurological disorders (including concussion) that might impact neurological and behavioral performance, and no medications (other than birth control); and (3) smokers who have self-reported smoking for at least 0.5 year and presently smoked an average of 4 or more cigarettes per day. Most cigarettes delivered at least 0.5 mg nicotine (by FTC method). Exclusion criteria were: (1) persons acutely under the influence of any medicine, prescription or over-the-counter drug, including antihistamines and pain relievers; (2) self-report of illicit substance use; (3) self-report of alcohol ingestion; (4) medical problems that might affect neurological and behavioral performance; (5) hearing deficits as assessed by a standard hearing test; (6) abnormal EEG or substantial electroocular (EOG) activity; and (7) close family members who had been diagnosed with schizophrenia or other major psychotic disorders.

The Institutional Review Board of Virginia Tech approved the study before data collection began. Advertisements were posted to recruit healthy teenage girls from the southwestern Virginia counties of Montgomery, Pulaski, Giles and Floyd, including the towns of Blacksburg, Christiansburg, Floyd, Pulaski, Radford, and Pearisburg. Prospective participants and their parents/guardians were told about the study and their
questions were answered in a telephone interview. If a girl met the qualifications, she and her parent/guardian were mailed a consent form for the parent (see Appendix A), an assent form for the girl (see Appendix B), and a medical questionnaire (see Appendix C).

Forty-nine participants were selected for the study, including 24 smokers (age: $M = 16.73$, $SD = 1.32$) and 25 non-smokers (age: $M = 16.24$, $SD = 1.27$). Of the smokers, 18 were White, non-Hispanic, two were African-American, one was Native American, and one was Hispanic-Native American. Of the non-smokers, 22 were White, non-Hispanic and three were African-American. Two smokers who reported current drug use were removed from all data analyses.

2. Blood Draw

On the experiment day, girls were shown the laboratory and all questions were answered. Smokers were informed that they could smoke before, but not during the experiment. Participants were paid $15 per hour; the experiment was expected to take 2-3 hours per participant.

After the teenage girl and her parent/guardian signed for blood draw, a licensed phlebotomist withdrew 8 mL blood from the upper arm for the assessment of MAO-B. The blood sample was coded with a subject number and no name attached, and was sent to the Department of Chemistry for assaying.

3. CO Level Test

CO levels were assessed with a Micro-Smokelyzer CO monitoring device (Bedfont Scientific Ltd, Model 3A).
4. EEG/ERP Measurement

EEG/ERP measurement was conducted in the Cognitive Neuroscience Laboratory. Participants sat alone in a comfortable chair in the experimental room, and were fitted with a cap (Electrocap Inc.) with 30 electrodes (impedance < 5KΩ) referenced to the nose, plus vertical (above and below the left eye) and horizontal EOG electrodes. Skin underlying the electrodes was cleaned with Nuprep® cream and electrodes were filled with Electrogel® gel. Continuous EEG (0.1 to 100 Hz, 500 Hz sampling rate; gain of 150) was recorded and digitized with a Neuroscan® SynAmps amplifier and Scan® (version 4.2) EEG software.

Sixty-second eyes open and eyes closed resting EEG was recorded before and after the P50 paradigm. During the P50 paradigm, participants attended to a stationary cross (+) on the computer monitor screen at eye level, which was 80 cm in front of them. 40 identical pairs of 1ms 1000 Hz sinusoidal tone pips (1ms rise/fall; 70dB), with a 512 ms inter-click interval and 10000 ms inter-pair interval, were delivered by the Neuroscan® stimulus generation system through speakers placed 35 cm from each ear.

5. Cognitive Tests

After having the EEG recording, cap removed and taking a break, participants performed four computerized tasks: ANT test, Stroop test, N-back Memory Test, and Reading the Mind in the Eyes test.

(1) **Attention Network Test** (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002). During ANT, participants were asked to identify the direction (left or right) of the central arrow in a row of five arrows, by clicking the left or right key of the computer with the left
and right index finger. The ANT evaluates three separate attention effects. Three conditions are used to evaluate the alerting effect: no cue, center cue and orienting cue (cues were star markers in the screen). To evaluate the orienting effect, the row of five arrows was shown above or below a fixation point on the screen. To measure the conflicting effect, the central arrow was accompanied by four arrows of the same (congruent condition) or different (incongruent condition) direction. The ANT program automatically computes and displays the alerting, orienting and conflict effects, the mean reaction time (RT), and accuracy. Total time for this task was about 30 minutes.

(2) Stroop Test (Lezak, 1995). This test measures the ability to focus attention and to reduce conflict. Participants were asked to identify the color of the symbol or the word on a computer screen by clicking the corresponding keys with right and left index fingers. In the first section, there were 60 trials of colorful symbols (XXXX). In the second section, there were 80 trials of incongruent information: the word 'red' written in three colors except red, the word ‘green’ written in three colors except green, and so on. In the third section, there were 80 trials with congruent information. There were four types of trials: the word ‘blue’ written in blue, the word ‘yellow’ written in yellow, and so on. The Stroop program calculates and displays the mean RT, standard deviation, and number of correct trials of each section. Total time for this task was about 30 minutes.

(3) N-back Task (Phillips, 2003). The 0-, 1-, and 2-back conditions of this task were used. A practice block preceded the experimental block. Stimuli were in upper and lower case letters. The task was to respond to the target letter presented at the beginning of each block (e.g., T) to indicate whether the presented letter (e.g., T or f) was the target
letter or not. This was done by hitting keys on a response box for yes or no. Percentage correct and RT between stimulus presentation and response were recorded. This task required about 30 minutes.

(4) Reading the Mind in the Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). This test assesses the ability to recognize expressed thoughts, desires, and goals from other's eyes. For each of 38 pairs of eyes, four words represented different complex emotions. Participants were asked to choose one word for the best description of the mind in the eyes. All emotion words were defined in sentences on an accompanying sheet. Participants were encouraged to read these definitions if they were unsure of the meaning of a word. This task required about 60 minutes.

6. Questionnaires

After EEG measurement and cognitive tasks, each participant was administered the following questionnaires:

(1) Fagerström Test for Nicotine Dependence (Fagerström, 1987; Heatherton, Kozlowski, Frecker, & Fagerström, 1991; see Appendix D). This questionnaire is a standard instrument for assessing the intensity of nicotine dependence in adults. The questions pertain to physiological and psychological feelings from ingesting and abstaining from nicotine.

(2) Tobacco Use History and Patterns Questionnaire (Colby et al., 2005; see Appendix E). This questionnaire assesses the duration and quantity of smoking cigarettes and other tobacco products, attempts to quit smoking, the method used for smoking and the expectation to continue smoking or quit in the future.
(3) **Differential Attention Processes Inventory** (DAPI; Grumbles & Crawford, 1981; Crawford, Brown, & Moon, 1993; see Appendix F). The DAPI consists of 40 self-descriptive statements about experiences of focused attention and ignoring distractions, as well as experiences of carrying out two tasks simultaneously. There are four subscales: (1) Moderately Focused Attention, which assesses the perceived ability to sustain moderately focused attention; (2) Extremely Focused Attention, which assesses the perceived proclivity to engage total attentional resources in task at hand, to the exclusion of outside stimuli; (3) Dual Attention Cognitive-Cognitive, which assesses the ability to conduct the dual cognitive attention tasks simultaneously; and (4) Dual Attention Cognitive-Physical, which assesses the ability to conduct the cognitive and physical attention tasks simultaneously.

(4) **Cognitive Failures Questionnaire** (CFQ; Broadbent, Cooper, FitzGerald, & Parkes, 1982; see Appendix G). This questionnaire consists of 28 self-descriptive items about experiences of attention and involvement in a variety of cognitive activities. The CFQ purportedly assesses frontal lobe functioning.

(5) **Annett Handedness Questionnaire** (Annett, 1967; see Appendix H). This questionnaire assesses to what degree the left or right hand is used when doing 12 different activities.

(6) **Early Adolescent Temperament Questionnaire, Revised Short Form** (Ellis & Rothbart, 2001; see Appendix I). For each of 65 statements, participants were asked to rate how accurately the statement described them. There are two subscales of behaviors (activation control and affiliation) and 10 temperament types; attention, fear, frustration,
high intensity pleasure/urgency, inhibitory control, pleasure sensitivity, perceptual sensitivity, shyness, aggression, and depressive mood.

(7) Schizotypal Personality Questionnaire (SPQ; Raine, 1991; see Appendix J). This questionnaire measures schizotypal personality. There are nine subscales: ideas of reference, excessive social anxiety, odd beliefs or magical thinking, unusual perceptual experiences, odd or eccentric behavior, no close friends, odd speech, constricted affect, and suspiciousness.

7. Perception Tests

Finally, each participant was administered taste and smell tests.

(1) Perceived Bitterness of 6-n-propylthiouracil Test (PROP; Enoch et al., 2001). PROP is chemically related to phenylthiocarbamide (PTC). Participants were instructed to place a little cotton sheet containing PROP on their tongue and state if they tasted something or not. If they tasted something, they were asked to describe the taste and then rate the strength of this taste from 0 (do not experience anything) to 10 (very bitter).

(2) Brief Smell Identification Test (R.L. Doty, Sensonics, Inc., Haddon Heights, NJ). This is a 12-item test for measuring olfactory function. Participants were presented 12 types of smells and asked to identify the smell from four alternative choices.

8. ERP Data Processing

ERP raw data were processed offline with NeuroScan® version 4.2. Continuous EEG was epoched offline from -50 ms to 462 ms. Epochs were then detrended and baselined the 50 ms pre-stimulus period. To eliminate gross eye movement, muscle and movement artifact, epochs were submitted to automatic artifact rejection (±50 μV for eye
channels, FP1, FP2, F3 and F4). Epochs were then visually verified by two independent experimenters and further observed muscle, movement and eye artifacts were removed. Separate averaged evoked potentials (EPs) were created for the S1 and S2 for each participant. To better image the early components, a two-pole Butterworth digital filter (band-pass 10-70 Hz, 24 dB per octave roll-off) was applied to the averaged EPs.

Averaged evoked potentials were exported into Brain Vision Analyzer® (Brain Products, Germany). A semi-automatic program identified N40 (30-60 ms) and P50 (45-80 ms) peak amplitudes and latencies for the following regions: frontal (F3, Fz, F4), fronto-central (FC3, FCz, FC4), central (C3, Cz, C4), centro-parietal (CP3, CPz, CP4), and parietal (P3, Pz, P4). Two experimenters verified peaks separately and adjusted them when necessary. The experimenters were blind to the smoking status of the participants. The peak values (µV) were exported to Microsoft Excel®.

9. Cognition, Perception and Questionnaire Data Processing

All cognition data derived automatically from the ANT, Stroop and N-back tests were exported to Microsoft Excel®. Data from the Mind in the Eyes Test, questionnaires and perception tests were entered into Microsoft Excel® directly by students in the lab.

10. Platelet MAO-B Assay

Venous blood samples (8 mL) were obtained from healthy participants. VacutainerÆ collection tubes (75 mm) contained 0.057 mL of 0.34 M potassium EDTA as an anticoagulant. Platelet rich plasma (PRP) was prepared immediately after collection by centrifugation in an AllegraTM 21R Centrifuge at 200 x g for 10 min at room temperature. The PRP from each participant was pooled in a polypropylene tube, taking care to not
disturb the sedimented red cells and the buffy layer. Aliquots of 20 µL were removed for platelet counting and the remainders of each sample were stored at -70°C. PRP samples were diluted in two steps with Isoton to a final 1:5005 dilution prior to the platelet counting on a Coulter Z2 Particle Count & Size Analyzer (Beckman Coulter, Inc. FL, USA), using a 50 µm aperture. Particle size limits were set to 1.8 - 31.5 µm³, corresponding to particle diameters of 1.5 - 4.0 µm. All platelet counts were done within 90 minutes from the time the blood was drawn. The reported platelet count was an average of three readings.

After thawing, PRP samples (100 µL containing 10⁹ platelets/mL) were preincubated with 0.1 M sodium phosphate buffer, pH = 7.4 (150 µL in 1.5 mL Eppendorf® tubes) for 15 min in a gently agitated water bath at 37°C. Addition of a pre-warmed substrate solution (250 µL 4 mM in 0.1 M sodium phosphate buffer, pH 7.4, final concentration of 2 mM) initiated the reaction. After a 1 hour incubation period, the reactions were terminated by adding 30 µL of 70%, (w/w) aqueous HCIO₄. The solutions were vortex-mixed and the precipitated proteins were sedimented at 20,500 x g for 10 min at 10°C. Fractions of the resulting supernatants (350µL) were transferred to a quartz cuvette and analyzed on a Beckman DU7400 diode array spectrophotometer or stored at 4°C if not analyzed immediately. UV-VIS scans from 300 nm to 600 nm were obtained and the intensities of the absorbance at 420 nm were recorded. For each participant, triplicate samples analyses and one blank analysis were performed. The blank was incubated following the same experimental conditions as the samples except that the substrate solution was added after the addition of HCLO₄. The background absorbance could be subtracted by scanning the blank sample.
Chapter 3
Psychophysiological Vulnerabilities of Female Teenage Smokers

1. Previous Analysis

To identify the psychophysiological vulnerabilities of female teenage smokers, comparisons on these measures were conducted between smokers and non-smokers. Smokers were then divided into high and low dependent groups with Fagerström Test for Nicotine Dependence. Comparisons were conducted between these groups; the results are reported below.

2. Results

2.1. CO Level

On the day of the experiment, 19 of the 24 smokers reported that they smoked their own cigarette before they came to the lab. The CO breath level of smokers (11.27 ± 8.85 ppm; range 0-35) was higher than non-smokers (0.64 ± 0.70 ppm; range 0-2), t (45) = -5.99, p < 0.001 (Figure 1). This demonstrated the effect of smoking on breath CO level.

Smokers were divided into high and low dependent smokers at the median of Fagerström Test for Nicotine Dependence (4 to 7 is the high dependent, 0 to 3 is the low dependent). High dependent smokers (N = 10, 16.60 ± 9.89 ppm) had significantly higher CO levels than the low dependent smokers (N = 12, 6.83 ± 4.73 ppm), t (20) = 3.14, p = 0.005 (Figure 2).

2.2. Sensory Gating

Sensory gating was calculated by the S2 (P50 - N40)/S1 (P50 - N40) ratio. P50 - N40 is the amplitude difference between the N40 negative component and the P50 positive
component of the averaged evoked potential. The lower the value, the better the sensory gating is. Grand averaged evoked potentials for smokers and non-smokers were shown in Figure 3.

No significant difference in sensory gating between smokers and non-smokers was found for each of the 15 electrode sites. The mean value of sensory gating (15 sites) for smokers was 0.54 ± 0.31, the mean value for non-smokers was 0.58 ± 0.44 (Figure 4).

No difference in sensory gating was found between the low and high dependent smokers. The mean value of sensory gating (15 sites) for the high dependent smokers was 0.62 ± 0.31, the mean value for the low dependent smokers was 0.47 ± 0.30 (Figure 5). These results were unlike those of Crawford et al. (2002)'s, which showed that smokers had better sensory gating function than non-smokers. A possible reason for this discrepancy is that participants in Crawford et al. (2002) were heavy users with a history of smoking at least five years.

2.3. Cognitive Tests

(1) ANT: In the three attention systems (alert, orienting, and conflict), there were no significant differences for performance between smokers and non-smokers. However, the high dependent smokers (691.70 ± 53.86 ms) showed significantly longer overall reaction time than did the low dependent (570.67 ± 53.58 ms) across the three conditions, \( t(20) = 5.26, p < 0.001 \) (Figure 6).

(2) Stroop Test: In the three conditions (control, congruent, and incongruent), there were no significant differences in RT for each condition between smokers and non-smokers, \( F(1, 45) = 3.93, p < 0.08 \). However, the high dependent smokers (734.14 ±
63.40 ms) showed significantly longer overall reaction time than did the low dependent (646.92 ± 85.84 ms), F (1, 20) = 5.25, p < 0.05 (Figure 6).

(3) N-back Task: No significant differences in performance or RT were found between smokers and non-smokers. Similar to the other tasks, the high dependent smokers (343.56 ± 73.02 ms) showed significantly longer overall RT than did the low dependent (232.08 ± 118.98 ms), F (1, 16) = 5.42, p < 0.05 (Figure 6).

(4) Reading the Minds in the Eyes Test: Smokers (23.18 ± 5.22) had more difficulty in recognizing complex emotions in the eyes than did non-smokers (26.08 ± 4.62), t (45) = 2.02, p < 0.05 (Figure 7). Among smokers, the high dependent (20.30 ± 5.77) had more difficulty in recognizing the complex emotions than did low dependent (25.58 ± 3.32), t (20) = 2.69, p < 0.02 (Figure 8).

In summary, there was no significant difference in cognitive performance across the ANT, Stroop, and N-back tasks between smokers and non-smokers. However, among smokers, the high dependent consistently showed longer RTs in these tasks. Smokers did have more difficulty than non-smokers with the Reading the Minds in the Eyes test, and this effect was mirrored in comparing high and low dependent smokers. These data collectively do not indicate that smoking is a moderator of cognitive performance. However, among smokers, high dependency is associated with longer RT. Additionally, smoking had a negative association with perceiving emotions in the eyes of others.

2.4. Smell and Taste

(1) PROP Taste Test: Fewer smokers (72.7%) than non-smokers (96%) could taste PROP as being bitter, X^2 (1) = 5.00, p < 0.03. Almost all non-smokers reported this
bitterness to be strong. This result supported previous findings that showed smokers are less sensitive to these chemicals than non-smokers (Enoch et al., 2001).

(2) **Smell Identification Test**: There were no differences between smokers and non-smokers.

### 2.5. Questionnaires

1. **Schizotypal Personality Questionnaire**: Smokers (23.24 ±12.20) did not differ significantly from non-smokers in the total schizotypal score (26.56 ± 12.80). However, smokers (2.19 ± 1.83) reported significantly more odd beliefs or magical thinking than non-smokers (1.08 ± 1.19), and smokers (1.95 ± 1.66) reported less excessive social anxiety than non-smokers (3.76 ± 2.42), $t(44) = -2.48$ and 2.90 respectively, $p < 0.05$ (Figure 9). The two groups did not differ significantly on the three factors of cognitive-perceptual deficits, interpersonal deficits and disorganized thoughts.

   Among smokers, the high dependent reported significantly more odd speech (low: 3.00 ± 1.60; high: 6.33 ± 4.50) and constricted affect (low: 0.92 ± 1.24; high: 2.67 ± 2.67), $t(19) = 2.39$ and 2.85, $p < 0.05$ (Figure 10). There was a non-significant trend for high dependent smokers (10.33 ± 6.48) to report more interpersonal difficulties than low dependent (5.83 ± 4.26), $t(19) = 1.92$, $p = 0.07$.

   (2) **Early Adolescent Temperament Questionnaire**: Smokers (2.72 ± 0.89) showed less activation control than non-smokers (3.36 ± 0.56), $t(45) = 2.98$, $p = 0.005$. Smokers (3.15 ± 0.47) showed a lower score on attention than non-smokers (3.54 ± 0.42), $t(45) = 3.02$, $p < 0.005$. Smokers (3.51 ± 0.50) also showed a lower score on inhibitory control than non-smokers (3.82 ± 0.43), $t(45) = 2.25$, $p < 0.05$. There was a non-significant trend
for smokers (3.65 ± 0.63) to more frustration than non-smokers (3.33 ± 0.55), t (45) = 1.88, p = 0.07. These differences collectively suggest that smokers showed more difficulty with executive control than non-smokers. Smokers also showed a greater score on the perceptual sensitivity scale (3.84 ± 0.55) than non-smokers (3.50 ± 0.47), t (45) = 3.05, p < 0.005 (Figure 11).

High dependent smoking reported significantly more aggressive feelings (2.68 ± 0.43) than low dependent (2.07 ± 0.43), t (19) = 2.28, p < 0.05. The high dependent group reported significantly less pleasure sensitivity (2.96 ± 1.01) than low dependent (3.88 ± 0.71), t (19) = 2.53, p < 0.05 (Figure 12).

(3) **Differential Attentional Processes Inventory**: There were no significant differences between smokers and non-smokers or between low and high dependent groups on the four subscales.

(4) **Cognitive Failures Questionnaire**: There was no significant difference between smokers and non-smokers or between low and high dependent groups.

2.6. Smoking Dependency

(1) **Parental Smoking Status**: Of the non-smokers, 28% of the parents (N = 7; 1 both, 6 fathers only) smoked presently, whereas 68% of the smoker’s parents (N = 15; 3 mother only, 4 father only, 8 both) smoked presently. Additional parents in both groups had smoked in the past but had quit.

(2) **Amount of Smoking**: The mean number of cigarettes smoked per day was 11.91 ± 8.22, ranging from 4 to 40, and 11 reported 10 or more cigarettes per day.
(3) **Age of Starting to Smoke**: Smokers reported the mean age of starting to smoke was 13.68 ± 3.01 years, ranging from 7 to 17 years. The mean number of years smoking was 3.15 ± 2.22, ranging from 1 to 8 years. The mean age at which they began to smoke daily was 14.61 ± 2.40, ranging from 9 to 17 years.

(4) **Smoking Dependency**: On the Fagerström Test for Nicotine Dependence with a maximum score of 10, smokers ranged from 0 to 7, with a mean value of 3.41 ± 2.30. For this scale, 7 to 10 points is highly dependent, 4 to 6 points moderately dependent, and less than 4 points minimally dependent. Thus, 45% of these smokers were moderately to highly dependent on smoking in the study.

(5) **Tobacco Use History and Patterns Questionnaire**: When asked, "How likely would you be a non-smoker one year from now?", their responses were not all likely (22.7%), a little likely (36.4%), somewhat likely (27.3%), pretty likely (0%), or very likely (9.1%). When asked "How much would you like to quit smoking?", their responses were not all (13.6%), a little (22.7%), somewhat (18.2%), pretty much (13.6%), and very much (27.3%). When asked "If you try to quit smoking in the next month, how successful do you think you would be?", responses were not at all (13.6%), a little bit (36.4%), somewhat (31.8%), quite (13.6%), and very (0%). When asked "If you try to cut down on your smoking in the next month, how successful do you think you would be?", responses were not at all (13.6%), a little bit (18.2%), somewhat (22.7%), quite (31.8%), and very (9.1%). These results showed that a number of the girls did not think they would quit or reduce levels of smoking successfully.

2.7. Platelet MAO-B Activity
Smokers (1.38 ± 0.31 nmoles; range 0.84 - 1.96 nmoles of 1-methyl-4-(1-methyl-2-pyrrolyl)-2, 3-dihydropyridinium ion formed/10^9 platelets/minute) had significantly lower platelet MAO-B activity than non-smokers (1.59 ± 0.37 nmoles; range 0.95 - 2.24 nmoles), t (43) = 1.97, one-tailed; p < 0.05 (Figure 13). Hence, smoking seemed to reduce platelet MAO-B in this group of teenage girls.

Comparison between the high and low dependent smokers found that there was no significant difference on MAO level between the high (1.32 ± 0.23 nmoles) and low dependent smokers (1.44 ± 0.37 nmoles; Figure 14).

3. Psychophysiological Vulnerabilities of Female Teenage Smokers

In summary, female teenager smokers showed some psychophysiological vulnerabilities in the study. For example, smokers reported more odd beliefs or magical thinking than non-smokers. Smokers also reported more difficulty in executive control and inhibition, and had more problems in identifying others' emotions on their faces, than did non-smokers. Smokers did not show poorer cognitive performance on the Stroop, ANT, and N-back tasks. There were no significant differences in sensory gating between smokers and non-smokers.

Comparisons between high and low dependent smokers revealed that the high dependent group reported more odd speech and constricted affect, and more aggressive feelings. The high dependent group also had slower reaction times on all cognitive tests and showed less ability to recognize facial expressions. Additionally, the high dependent smokers started smoking at a younger age and smoked more cigarettes per day.
In some, the above comparisons provide some, albeit mixed support for smoking issues discussed in Chapter 1. For example, the augmenting effects of smoking on attention and executive functioning may increase its usage among patients with schizophrenia and ADHD. Moreover, teenage smokers with existing cognitive deficits may use smoking to enhance cognitive function. Some, but not all of the self-reported measures in the present study were consistent with these notions. Furthermore, smoking did not differentiate performance on the Stroop, ANT, and N-back tasks, but high dependent smokers did show a consistent trend toward longer RTs on these tasks in comparisons with low dependent smokers. There were no significant differences in sensory gating between smokers and non-smokers. Smokers did have more difficulty in emotion identification, an effect that was amplified in the high dependent group. Collectively, these findings suggest some cognitive and affective problems to be associated with female teenage smoking, although the data do not provide entirely consistent support for these deficits.

These findings raise the following questions: (1) To what degree are the brains of teenage females still developing? (2) To what degree does chronic administration of nicotine lead to changes in the brain, both reversible and non-reversible? and (3) What are the correlations among the variables in the present study. Although much research remains to be conducted on question (1), current knowledge holds that frontal lobe development continues well into adolescence (Goleman, 1995, pp. 352). In regard to question (2), some studies found that smoking increased the density of neuronal cholinergic nicotinic receptors (Perry, Davila-Garcia, Stockmeier, & Kellar, 1999) and
reduced monoamine oxidase A and B (see Yu & Boulton, 1987; Fowler et al., 1996a, b). Hence, the possibility exists that smoking may alter adolescent brain development. Analyses presented in Chapter 4 explore the possible role of MAO activity in the relationship between smoking and the adolescent brain by exploring differences between high and low MAO-B groups among teenage female smokers. Question (3) is addressed by correlation analyses presented in Chapter 5.
Chapter 4
Comparisons between High and Low MAO Groups

1. Background

The interest in comparing high and low MAO-B individuals emerges from evidences: that platelet MAO-B level is nicotine dose-dependent, as will be discussed below. In the present study, 45% of smokers were classified as moderately to highly dependent on smoking. Significant differences were found between high and low dependent smokers on ANT, Stroop, N-back, Reading the Eyes in the Mind tests, and the Schizotypal Personality and Early Adolescent Temperament Questionnaires. The smoking group could also be divided into high and low MAO groups to see if similar effects are found as between low and high dependent smokers.

Dose-dependent decreases in platelet MAO-B from smoking have been found in some studies. A negative association between smoking and platelet MAO-B was demonstrated in a sample of 383 healthy students (193 males, 190 females) (Propping, Rey, Friedl, & Beckmann, 1981). Platelet MAO-B activity has been found to negatively correlate with the number of cigarettes smoked per day in female, but not male smokers (Yong & Perry, 1986). A significant negative correlation between MAO activity and thiocyanate concentration was observed in female smokers \( r = 0.43, n = 36 \) but not for male smokers \( r = 0.02, n = 31 \) (Norman et al., 1987). A genetic study of alcoholism suggested a dose-dependent decrease in platelet MAO-B levels in current smokers, with smoking amount measured by the number of cigarettes smoked per day (Saccone et al., 1999). However, these decreases have been reported to be normalized when smokers
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quit (Berlin, Spreux-Varoquaux, & Launay, 2000). Platelet MAO-B activity has also been
reported to inversely relate to plasma cotinine concentration, which is an indirect index of
tobacco use (Berlin et al., 2000). Although in Berlin et al. (2000), the number of cigarettes
smoked per day and the Fagerström Tolerance Questionnaire score were not reported to
associate with MAO-B level, researchers suggested a further work on whether platelet
MAO-B activity can be used as a reliable marker of tobacco smoke exposure.

Some drug studies have found that MAO inhibitors can affect cognitive performance.
MAO inhibitors such as amitriptyline, dothiepin, mianserin and trazodone impair attention
and ability to concentrate in elderly patients (for review, see Knegtering, Eijck, &
Huijsman, 1994). However, other drug studies found that both MAO-A and MAO-B
inhibitors present cognitive enhancing properties and they may be useful in treatment of
cognitive disorders (for review, see Delumeau et al., 1994).

Links between MAO activity and personality and psychopathology have also been
reported. For example, in comparisons of patients with chronic schizophrenia, their
first-degree relatives, and control participants, MAO activity was significantly lower in
patients than in control participants, and lower in ill relatives than in non-affected relatives
within families (Baron et al., 1984). MAO activity hence has been suggested to be a
heritable and stable trait within families. Studies have also found that alcoholics have
lower platelet MAO-B, and this effect is mainly confined to alcoholics with substance
abuse and impulsive, sensation seeking and extraverted personalities (Wiberg, Gottfries,
& Oreland, 1977, von Knorring & Oreland, 1985). Platelet MAO-B has been reported to
be significantly lower in Type 2 alcoholics than in Type 1 alcoholics (Hallman, von
Type 1 alcoholics are characterized by a late onset of drinking problems and few social complications, while the type 2 alcoholics have an early onset of drinking problems and multiple social complications (Cloningber, Bohman, & Sigvardsson, 1981). Type 2 alcoholics had significantly higher frequencies of self-defeating, schizotypal, antisocial and borderline personality disorders than Type 1 alcoholics. However, no correlation was found between platelet MAO-B and DSM-III-R defined personality disorders in the study.

2. Hypothesis

Comparisons between the high and low MAO groups may help further understand the effect of smoking on the brain and behavior. For this purpose, the smokers were divided into two groups as the between-subject factor for independent sample T-tests: high and low platelet MAO-B level. Alpha was set at < 0.05 for significance, and Bonferroni corrective tests were used to control Type 1 error. To enhance the focus of these comparisons, six relevant measures were selected as dependent variables for contrasts: Sensory Gating, Attention Network Test (ANT), Schizotypal Personality Questionnaire (SPQ), Differential Attentional Processes Inventory (DAPI), PROP taste test, and smoking dependency. Hypothesis for each measure are described as follows.

2.1. Sensory Gating

In the primary analyses, no significant differences in sensory gating between smokers and non-smokers, nor between low and high dependent smokers, were found for each of the 15 electronic sites. In contrast, Crawford et al. (2002)'s reported that smokers had better sensory gating than non-smokers. Participants in the latter study
were heavy users with a history of smoking at least five years. Smokers in the present study smoked for an average of three years with a range of one to eight years. Based on evidence described above that relates MAO activity to smoking, cognitive performance, and personality/psychopathology, as well as the findings of Crawford et al. (2002), a significant difference in sensory gating between high and low MAO groups was predicted in the present study. Reducing MAO may increase brain DA activity, resulting in better sensory gating in the high dependent smokers. This comparison may help clarify the discrepant findings of the primary analyses and Crawford et al. (2002) regarding smoking and sensory gating.

2.2. Attention Network Test (ANT)

In the previous analyses of ANT, Stroop and N-back data, high dependent smokers showed significantly longer RTs than low dependent. Therefore, the low MAO-B group was hypothesized to show longer RTs on the ANT than the high MAO-B group. Because reduced MAO may reflect improved cognitive performance by enhancing DA activity, the low MAO-B group was also hypothesized to perform better on the ANT.

2.3. PROP Taste Test

No specific study about the relationship between MAO-B and smell and taste has been conducted before. Smokers have been found to show less sensitivity to PROP than non-smokers (Enoch et al., 2001). In this study, fewer smokers (72.7%) than the non-smokers (96%) could taste PROP as being bitter with the PROP taste test. Almost all non-smokers reported bitterness to be strong. Based on previously described evidence of the dose-dependency between nicotine and platelet MAO-B, and the primary findings
on smoking and smell-taste sensitivity, the low MAO group was hypothesized to show less sensitivity to PROP than the high MAO group.

2.4. Schizotypal Personality Questionnaire (SPQ)

In previous comparisons, the high dependent smokers reported significantly more odd speech, constricted affect and interpersonal difficulties than low dependent smokers. Therefore, the low MAO group was also predicted to show more schizotypal characteristics than the high MAO group.

2.5. Differential Attentional Processes Inventory (DAPI)

No significant finding on DAPI scores was reported between smokers and non-smokers and between the high and low dependent smokers in the previous comparison. Therefore, no significant finding in DAPI is expected in the comparison between high and low MAO groups in the study.

2.6. Smoking Dependency

Dose-dependent decreases in platelet MAO-B activity have been reported in some studies before. The high dependent smokers in the present study reported smoking more cigarettes than did the low dependent. Therefore, the low MAO group was predicted to show greater smoking dependency than the high MAO-B group.

3. Analyses and Results

All smokers were first divided into high and low MAO groups. Independent sample T-tests were then conducted between two groups on sensory gating, ANT, SPQ, DAPI, PROP and smoking dependency. Results are reported as follows.

3.1. Distribution of MAO among Smokers
There were a total of 22 smokers in the present sample. Platelet MAO level ranged from 0.84 to 1.96 nmoles, with the mean value of 1.38 nmoles and the median value of 1.40 nmoles. The distribution of MAO activity is shown in Figure 15. The smokers were then divided into low MAO (0 – 1.40 nmoles; N = 11) and high MAO (> 1.40 nmoles; N = 11) groups. Comparisons on six measures between low and high MAO groups were conducted.

3.2. Sensory Gating

Sensory gating was measured for 15 electronic sites: Fz, FCz, Cz, CPz, Pz, F3, FC3, C3, CP3, P3, F4, FC4, C4, CP4, and P4. Each participant had 15 sensory gating values. The mean of these 15 sensory gating values was calculated for each participant, and this value was compared between low and high MAO groups. A significant difference on averaged sensory gating between these two groups was found, t (20) = 2.11, p < 0.05. The low MAO group had a mean value of 0.67 ± 0.34 μV; the high MAO group had the mean value of 0.41 ± 0.23 μV (Figure 16). Because a low value means better sensory gating, the high MAO group had better sensory gating than the low group.

3.3. Other Measures

No significant differences between the low and high MAO groups on the ANT, SPQ, DAPI, PROP, and Smoking Dependency measures were found.

4. Discussion

In this section, present results are discussed in the context of the hypotheses and previous studies. The major finding, which is about MAO and sensory gating, will be further discussed in Chapter 6.
4.1. Sensory Gating in High and Low MAO Groups

Among smokers, the analysis found a significant difference on sensory gating between these two groups; high MAO group had better sensory gating function than low MAO group. Little evidence can be found in the literature to show a direct relationship between MAO and sensory gating. Only two indirect studies related to MAO and sensory gating can be found: Crawford et al., (2002) and Riba, Rodriguez- Fornells, & Barbanoj (2002b).

Crawford et al. (2002)'s study explored the effects of smoking tobacco on sensory gating, P50 and stimulus-bound gamma band oscillations (GBO; 32–48 Hz) in auditory evoked potentials (50 tone pip pairs; 70 dB, 1000 Hz). Thirteen heavy cigarette smokers (20+/day) were tested after abstaining overnight and after smoking; thirteen age-matched non-smokers were tested twice without smoking. For P50 amplitude at the frontal region, there was a significant interaction between group and stimuli (S1, S2), F (1, 24) = 6.59, p = 0.017. Smokers exhibited greater P50 amplitudes than did non-smokers, F (1, 24) = 7.67, p = 0.011. Sensory gating was calculated by S1 (first stimulus) minus S2 (second stimulus) on P50 amplitude. Smokers exhibited significantly greater sensory gating differences (2.01 ± 1.36 µV) than non-smokers (0.89 ± 0.79 µV), F (1, 24) = 6.59, p = 0.017. Thus, smokers suppressed overall 43% amplitude from S1 to S2, whereas non-smokers suppressed overall 33%.

Two neurochemical pathways of smoking effects on sensory gating were suggested to explain these results. The first pathway is that nicotine stimulates release of DA via nicotinic receptors on DA neurons (Cooper et al., 1996). DA release then enhances
sensory gating. In this way, the effect is short-lived because nicotinic receptors
desensitize rapidly. The second pathway is that chronic inhibition of MAO leads to
greater DA bioavailability. Due to the greater intraneuronal DA levels, further production
of DA would be suppressed by the competitive inhibition of tyrosine hydroxylase. These
two mechanisms taken together would appear as a net DA antagonism effect and thus
produce greater sensory gating. No acute effect of smoking on sensory gating was found
In this study, suggesting that smoking exhibits a chronic effect on sensory gating.

However, the present analysis found that the high MAO group had better sensory
gating than low MAO group. Several differences between these two studies may explain
these apparently conflicting findings. First, smokers in Crawford’s study were older,
heavy smokers (age from 20 to 40 years; smoked 5+ years; presently smoked 20+
cigarettes per day), and smokers in the current study were younger, lighter smokers (age
from 14 to 18 years; smoked 0.5+ years; presently smoked 4+ cigarettes per day).
Differences in duration and level of smoking amount may have exerted variable,
inconsistent effects on the relationship between MAO and sensory gating. Secondly,
participants in Crawford’s study were all men, and participants in the current were
teenage girls. Thirdly, no comparison between high and low MAO groups was conducted
directly in Crawford et al. (2002)’s study. Therefore, the proposed theory can not be
verified by these two studies directly. More research needs to be conducted that
examines the effects of the duration and level of smoking on the relationship between
MAO and sensory gating.
Another study may provide insight into the present finding. Riba et al (2002b) assessed the effects of acute administration of ayahuasca on P50 suppression and pre-pulse startle inhibition (PPI) in humans. Ayahuasca is a South American psychotropic plant tea that contains the psychedelic agent and 5-HT$_{2A/2C}$ agonist N,N-dimethyltryptamine (DMT). The beta-carboline alkaloids contained in ayahuasca show MAO inhibiting properties (McKenna, Towers, & Abbott, 1984; Riba et al., 2002a). In a clinical setting, ayahuasca shows dose-dependent characteristics of the psychedelics, such as perceptual, cognitive and affective modifications (Riba et al., 2001). Ayahuasca also results in changes in spontaneous EEG which are similar to the EEG changes caused by some 5-HT$_2$ and D$_2$ agonists (Riba et al. 2002a).

Placebo and two different ayahuasca doses (0.6 mg and 0.85 mg DMT/kg body weight) were administered to eighteen healthy volunteers. They were 15 males and 3 females with mean age of 25.7 years and they has prior experiences with psychedelic drugs. P50 and startle reflex recordings were then recorded at 1.5 h and 2 h after drug intake, respectively. Sensory gating (on Cz) was measured by the difference between amplitude values (C-T) and percentage suppression [1-(T/C)] x100 under the three drug conditions. C and T represent two auditory stimuli of P50 paradigm under two conditions (Conditioning and Testing). For the difference amplitude variable (C-T), placebo reduced 2.12 ± 0.42 µV from C to T, ayahuasca reduced 0.93 ± 0.34 µV from C to T with the low dose and reduced 0.52 ± 0.31 µV from C to T with the high dose. This reducing effect was significant, $F(2, 28) = 4.96$, $p < 0.05$, which means ayahuasca impaired sensory gating as measured by difference amplitude values (C-T). For percentage suppression
[1-(T/C)] x 100, a significant drug effect on percentage suppression was observed, F (2, 28) = 4.78, p < 0.05. Placebo reduced 71.86 ± 8.41% from C to T, ayahuasca reduced 24.57 ± 17.17% with the low dose and reduced 6.00 ± 18.10% with the high dose. Overall, the results indicate that ayahuasca, as a type of MAO inhibitor, shows an inhibitory effect on sensory gating after the acute administration, and this inhibition may be dose-dependent. However, no direct relationship between platelet MAO level and ayahuasca administration was shown in this study, nor are there other extant studies that examine this relationship. Therefore, although these findings are consistent with the present ones, they do not provide direct support for them.

In conclusion, no evidence can be found to show the direct relationship between MAO and sensory gating from the previous studies. The finding of the current study may be the first report on the relationship between sensory gating and MAO. Because the relationship between MAO and sensory gating is the main finding of the current analyses, it will be discussed more broadly in Chapter 6.

4.2. ANT in High and Low MAO Groups

In the previous analysis with ANT, Stroop and N-back, high dependent smokers showed significantly longer overall RTs than low dependent. Because some studies suggested that MAO level is dose-dependent, high dependent smokers may fall into low MAO group. Therefore, the low MAO group was hypothesized to show both the longer RTs and better attention performances (due to greater DA activity) in ANT than the high MAO group. However, no significant finding was found between low and high MAO groups on ANT in the current analysis. The hypothesis was based on the assumption that
since MAO level is dose-dependent; the high dependent smokers would fall into the low MAO group. The result did not support this assumption. Thus, although MAO may be dose-dependent, it does not appear to be related to Fagerström test score.

4.3. PROP Taste Test in High and Low MAO Groups

The low MAO group was hypothesized to show less sensitivity to PROP than the high MAO group. This prediction was not supported, suggesting that among smokers, high and low MAO group have the similar taste sensitivity. Hence, previous reports of taste sensitivity deficits in smoking are not likely related to MAO activity.

4.4. SPQ in High and Low MAO Groups

In prior work, high dependent smokers reported significantly more odd speech, constricted affect and interpersonal difficulties than low dependent smokers. Therefore, the low MAO group was predicted to show more schizotypal characteristics than high MAO group among smokers. However, no significant differences between low and high MAO groups on SPQ were found in the current study.

Human MAO activity has been found to correlate with individual personalities and behaviors. Buchsbaum et al., (1976) first demonstrated that individuals with low MAO activity levels were more vulnerable to certain psychiatric disorders, such as schizophrenia and bipolar disorder. Subsequently, a relation between low activity of platelet MAO and alcohol addiction were reported; alcoholics had low levels of platelet MAO, and low platelet MAO activity was mainly confined to those alcoholics with substance abuse and with impulsiveness, sensation seeking and extraversion personalities (Wiberg et al., 1977, von Knorring et al., 1985). A relationship between low
activity of platelet MAO and personality characteristics such as sensation seeking, impulsiveness, monotony avoidance, and aggression, has also been found in healthy controls in some studies (for review, see Oreland, Hallman, & Damberg, 2004). However, none of these studies assessed the variable of smoking, and so these findings might not be directly comparable to the present ones.

4.5. DAPI in High and Low MAO Groups

Consistent with the hypothesis, no significant difference between low and high MAO groups on DAPI was found.

4.6. Smoking Dependency in High and Low MAO Groups

The low MAO group was predicted to show more smoking dependency than the high MAO group. However, no significant difference between low and high MAO groups on smoking dependency could be found as measured by the Fagerström Test.

Dose-dependent decreases in platelet MAO-B activity have been reported by some studies. For example, platelet MAO-B activity negatively correlated with the number of cigarettes smoked per day in female smokers, but not in male smokers (Yong & Perry, 1986; Norman et al., 1987). A dose-dependent (reported number of cigarettes smoked per day) decrease in platelet MAO-B levels in current smokers has been reported (Saccone et al., 1999). However, Berlin et al., (2000) reported that the number of cigarettes smoked per day and the Fagerström Tolerance Questionnaire score were not associated with MAO-B level. The current study is consistent with this finding. Smoking dependency was not different between high and low MAO groups with the Fagerström
Test among smokers. Therefore, MAO maybe dose-dependent, but unrelated to Fagerström Test scores.

5. Summary

In summary, comparisons on six measures between the high and low MAO groups yielded only one significant finding: a significant difference on sensory gating between these two groups. The high MAO group had a better sensory gating function than the low MAO group. Little evidence can be found in the literature to show the relationship between MAO and sensory gating, only two indirect studies related to MAO and sensory gating can be found (Crawford et al. 2002; Riba et al., 2002b).

Significant differences between two groups on ANT, PROP taste test and smoking dependency were also predicted. However, no significant difference could be found. Hypotheses were based on the following assumptions: (1) platelet MAO-B level is dose-dependent; (2) in the study, according to the Fagerström Test for Nicotine Dependence, 45% of smokers were moderately to highly dependent on smoking. The whole group could be divided into the high and low MAO groups; (3) previous analysis have found significant differences between the high and low dependent smokers on ANT, Stroop, N-back, Reading Minds tests, Schizotypal Personality and Early Adolescent Temperament Questionnaires. Dose-dependent decreases in platelet MAO-B activity have been reported by some studies before. However, the current analysis found that Smoking dependency was not different between high and low MAO groups with the Fagerström Test among smokers. Therefore, MAO may be dose-dependent, but unrelated to Fagerström Test scores.
Chapter 5
Correlations between MAO, Sensory Gating and other Measures

Correlational analyses were conducted following the contrast analyses in Chapter 4. First, sensory gating was correlated with each measure. After that, platelet MAO level was correlated with each measure. Significant relationships are hypothesized as follows.

1. Sensory Gating with other Measures

   Sensory gating reflects the filtering function of the brain, thereby promoting optimal attention and cognition. As such, sensory gating should show associations with other variables that are generally consistent with this notion. Pearson correlation analyses were conducted to verify each of the following hypotheses across all participants (N = 47), with p < 0.05 as the alpha level of significance.

1.1. Sensory Gating and MAO

   Crawford et al. (2002) reported that smokers have better sensory gating than non-smokers. It was suggested that smoking chronically reduces brain MAO activity, which in turn has an enhancing effect on CNS dopaminergic activity and sensory gating. Smokers have also been reported to have lower MAO-B activity than non-smokers (Castagnoli et al., 2004). Therefore, a negative correlation between platelet MAO-B level and sensory gating was predicted. The low MAO level would be associated with a better sensory gating function.

1.2. Sensory Gating and Cognition

   Sensory gating occurs in the preattentonal stage of information processing. In Wan et al. (in preparation), ANT and Stroop tests were administered to 39 undergraduate
students. Good sensory gating was found to correlate with better alerting, weaker conflict, shorter mean RT, and higher accuracy. Therefore, positive correlations between sensory gating and cognitive variables were predicted for the analysis.

1.3. Sensory Gating and Smoking Dependency

There is no direct evidence to show a relationship between sensory gating and smoking dependency. However, as suggested above, cigarette smoking may have a positive association with CNS dopaminergic activity, and so may show a similar relationship with sensory gating function. Therefore, a positive correlation between smoking dependency and sensory gating was predicted.

2. MAO with Other Measures

Functional brain imaging studies have shown that the brain responds to both acute and chronic administration of nicotine/smoking in a variety of ways (for review, see Brody, in press). Acute responses include: a reduction in global brain activity; activation of the prefrontal cortex, thalamus, and visual system; activation of the thalamus and visual cortex during visual cognitive tasks; and increased DA concentration in the ventral striatum/nucleus accumbens. Chronic responses include: decreased MAO-A and -B activity in the basal ganglia, and a reduction in α- and β-nicotinic acetylcholine receptor (nAChR) availability in the thalamus and putamen. Overall, both acute and chronic smoking tends to increase monoaminergic and cholinergic neurotransmission, thereby influencing cognition performance, personality, and emotion. Based on this evidences, the following predictions were made.
2.1. MAO and CO Level

High dependent smokers showed higher CO levels in the previous analysis. High dependent smokers may have lower MAO level. Therefore, a negative correlation between platelet MAO-B activity and CO level was predicted.

2.2. MAO and Cognition

Because smoking may enhance cognitive performances among smokers, a negative correlation between cognitive performance and platelet MAO-B activity is predicted.

2.3. MAO and Schizotypal, Temperament and Attentional Questionnaires

Many studies have shown a relationship between personality and platelet MAO-B, as discussed above. Negative correlations between platelet MAO-B with personality traits such as schizotypy and impulsiveness were therefore predicted.

2.4. MAO and Smoking Dependency

A negative correlation between platelet MAO-B activity and smoking dependency was predicted. The lower the MAO level, the higher the smoking dependency would be. The MAO level would also be correlated to the number of cigarettes per day.

3. Analyses and Results

Pearson correlation analyses were conducted on sensory gating, MAO, and other measures. Results are reported as follows.

3.1. MAO and Sensory Gating

Platelet MAO negatively correlated with the averaged sensory gating value ($r = -0.30$, $p = 0.05$; Figure 17). Because the low value represents better sensory gating, the results reflected a positive correlation between the MAO level and the sensory gating function.
3.2. MAO and Cognitive Tests

No significant correlation was found between MAO and performances in ANT, Stroop, N-back, DAPI tests.

3.3. MAO and Temperament

Negative correlations were found between MAO activity and Rothbart Frustration ($r = -0.29$) and Rothbart Perceptual Sensitivity ($r = -0.34$), $p = 0.05$ for both (Figures 18 and 19).

3.4. MAO and CO Levels

A negative correlation was found between MAO activity and CO level ($r = -0.36$, $p = 0.05$ (Figure 20).

4. Discussion

Significant correlations were found between MAO and sensory gating, temperament, and CO levels. Each association is discussed below.

4.1. Sensory Gating and MAO

The analyses revealed that MAO level was negatively related with the average value of sensory gating. Because the value of sensory gating is the ratio between S2 (P50-N40) and S1 (P50-N40), the low value means the good sensory gating function. The result suggested that the MAO level positively relates to the sensory gating function. This finding is consistent with the contrast between high and low MAO groups in Chapter 4. However, like that result, this finding was opposite to the hypothesis. The prediction was that low MAO level may relate to good sensory gating, and smoking may reduce MAO level and thereby enhance sensory gating. The current results do not support this account.
Since this unexpected relationship between MAO and sensory gating was the main finding from the current analyses; it will be discussed in depth broadly in Chapter 6.

4.2. Sensory Gating and Cognition

In a previous study from our lab, sensory gating showed a positive relationship with attentional variables as indexed by performance tests, including alerting, conflict, mean RT, and accuracy (Wan et al., in preparation). Therefore, positive correlations between sensory gating and cognitive variables were predicted. However, in the current analysis, no significant relationship between sensory gating and ANT, Stroop, and N-back tests were found. Comparing the two studies, an age difference was found. The mean age for participants in Wan et al. (in preparation) was around 19 years old, and the mean age for the current study was around 16 years of age. At these different ages, brain development may differ, which may account for the discrepant findings. Other demographic differences, such as gender, educational level, and socioeconomic status may have further made comparisons between the results more problematic. In sum, the results may have stemmed from a variety of differences between a relatively rural sample of teenage girls and a sample of college students including males and females. Further studies may need to consider such variables to clarify the relationship between sensory gating and attention.

4.3. Sensory Gating and Smoking Dependency

No prior study has directly examined the relationship between sensory gating and smoking dependency. As discussed above, the high dependent smokers smoked more cigarettes, which may be associated with increased activity in various brain
neurotransmitters, which in turn may have a positive effect on sensory gating. Therefore, positive correlations between smoking dependency and sensory gating were predicted. However, the current analysis did not show a significant correlation between sensory gating and smoking dependency as assessed by the Fagerström test. The results suggested that there is no direct relationship between sensory gating and smoking dependency. As with the non-significant effect of MAO level on smoking dependency reported above, this finding may reflect problems with the Fagerström test as an index of smoking level (Berlin et al., 2000).

4.4. MAO and CO Levels

A positive relationship between CO level and smoking dependency was reported in Chapter 3, but there was no evidence to show that high dependent smokers have lower MAO level from the previous analysis. However, a negative correlation was found between MAO activity and CO level in this study.

The measurement of breath CO level is an immediate method of assessing smoking status. A breath CO level of 10 ppm is usually considered as the cutoff between smokers and non-smokers (Nicholas, Marianne, & Jillian, 1981). After smoking inhalation, CO from cigarette displaces oxygen in the erythrocyte to form COHb. In this form, CO has a half-life of about 5 to 6 hours (Peterson & Stewart, 1970; Crowley, Andrews, Cheney, Zerbe, & Petty, 1989) and can remain in the blood for up to 24 hours, depending on factors such as gender, physical activity, and ventilation rate (Deller, Stenz, Forstner, & Konrad, 1992). While some exposure to CO may occur in daily life, such as environmental pollution, passive smoking and occupational exposure, the most likely
cause of high exposure is the smoking itself (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Salloajee, 1984).

There is little direct evidence in the literature on the relationship between MAO and CO levels. Research has suggested that cigarette consumption may lead to higher intake of CO, tar, and other harmful substances (Borgerding, Bodnar, & Wingate, 2000; Zhang et al., 2003). As discussed in Chapter 4, smoking more cigarettes may lead to a high CO level and a low platelet MAO level; the present negative association supports this assertion.

4.5. MAO and Cognition

A negative correlation between cognitive performance and platelet MAO-B activity was predicted. However, no significant correlation was found in the analysis. There has been little research which has directly examined the relationship between MAO and cognition. There are a few studies that link low MAO with adolescent attentional disorders, but virtually no studies exist in normative samples. It may be that those clinical studies do not directly bear on the present sample or attentional tests.

4.6. MAO and Schizotypy, Temperament and Attentional Questionnaires

Studies showed that some personality traits are related to platelet MAO-B activity, as was discussed above. Based on this evidence, negative correlations between platelet MAO-B and traits such as schizotypy and impulsiveness were predicted. Consistent with this prediction, negative correlations were found between MAO activity and Rothbart Frustration and Rothbart Perceptual Sensitivity in the current analysis.
A previous study found similar links between platelet MAO activity and temperament (Schalling et al., 1987). With the Eysenck Personality Questionnaire (EPQ), the Zuckerman Sensation Seeking Inventory, and the Karolinska Scales of Personality (KSP), low MAO-B group had higher scores in KSP Impulsiveness, EPQ Neuroticism, and KSP Somatic Anxiety and Irritability, and lower scores in KSP Socialization than did medium and high MAO-B groups. High MAO-B group scored lower in sensation seeking and conformity scales and higher in KSP Psychasthenia, Muscular Tension and Suspicion scales. Alcoholics, psychopaths, and suicide attempters tended to have low platelet MAO-B activity. The present findings fit this pattern of relationships between MAO and the temperament. MAO was negatively correlated with frustration and perceptual sensitivity, which is consistent with traits of impulsivity and sensation seeking reported above to have a similar relationship to MAO.

4.7. MAO and Smoking Dependency

A negative correlation between platelet MAO-B activity and smoking dependency was predicted. However, no significant correlation was found between them with Fagerström Test. No significant correlation was found between MAO level and the number of cigarettes per day. As discussed in Chapter 4, the assumption about MAO and dose-dependency may be not correct under the situation of the current study. Dose-dependent decreases in platelet MAO-B activity have been reported by some studies before, but the current study can not support this assumption directly. However, the current study found a negative correlation between CO and MAO levels. Smoking more cigarettes may lead to a high CO level and a low platelet MAO level. Therefore,
MAO maybe dose-dependent, but it does not appear to be related to the score on the Fagerström Test.

5. Summary

In sum, analyses revealed significant correlations between MAO and sensory gating, temperament, and CO levels. MAO was negatively related with sensory gating, suggesting that MAO positively relates to this function. This finding is consistent with the finding on sensory gating and MAO reported in Chapter 4, but opposite to the hypothesis. This hypothesis is based on the assumption that low MAO level relates to good sensory gating, and smoking may enhance sensory gating by reducing CNS MAO. The discrepant results of the present analyses will be discussed broadly in Chapter 6.

The present findings of relationship between MAO and temperament variables are generally consistent with the literature in this area. MAO appears to have a negative relationship with the traits of Frustration and Perceptual Sensitivity, which is consistent with previously reported negative associations between MAO and impulsiveness and sensation seeking.

A negative correlation was found between MAO activity and CO level in the study. Research has suggested that the consumption of cigarettes may lead to higher intake of CO (Borgerding et al., 2000; Zhang et al., 2003). Smoking more cigarettes may lead to a high CO level and a low platelet MAO level. Therefore, the results further verify the relationship between CO level and MAO activity.

Significant correlations between sensory gating and cognitive variables, and also smoking dependency, were predicted. These associations were not confirmed.
Significant correlations between MAO and cognition, schizotypy, and smoking dependency were also predicted, but not confirmed.
Chapter 6
MAO, Sensory Gating and Neurotransmission

The main finding in the current analysis is the unexpected relationship between MAO and sensory gating. Among smokers, the high MAO group had better sensory gating than the low MAO group, and among all participants, MAO level was positively correlated with sensory gating. Possible reasons for these findings are outlined below.

MAO is an enzyme that operates on brain neurotransmitters. Sensory gating is a filtering function of the brain and is measured with evoked cortical potentials. The effect of MAO on neurotransmitters may affect the ERP, thereby influencing sensory gating measurement. To explain the relationship between MAO and sensory gating, neurotransmitters related to both MAO and sensory gating are discussed in this chapter.

1. Monoamine Oxidase and Neurotransmission

1.1. Brain Distribution of MAO-A and MAO-B

Monoamine oxidase was first described as a tyramine-degrading enzyme in mammalian liver and was called “tyramine oxidase” (Hare, 1928). Subsequently, it was found in mitochondria in most peripheral tissues and the brain except erythrocytes; the name of the enzyme was changed to monoamine oxidase. Its main biological functions were suggested to be the detoxication of exogenous amines by oxidative deamination, because the enzyme was found to be very active in the gut and liver (for review, see Berlin & Anthenelli, 2001). There are two types of MAO: MAO-A and MAO-B, based on inhibitor selectivity (Johnston, 1968; Knoll & Magyar, 1972). MAO-A is selectively inhibited by clorgyline; it preferentially deaminates norepinephrine (NE), serotonin (5-HT)
and epinephrine (E). The highest concentrations of MAO-A are in the liver, gut and placenta; 70% of neuronal MAO is the type A. MAO-B is selectively inhibited by deprenyl (selegiline); it preferentially deaminates benzylamine and phenylethylamine (PEA). MAO-B is mainly found in glial cells and thrombocytes. MAO-A and MAO-B equally catabolize dopamine (DA) and tyramine (for review, see Palmer, 1998).

The human brain shows high MAO-A and MAO-B activity when compared to other organs containing MAO. The prevalence of MAO-B to MAO-A activity in the whole brain is approximately 2:1 (Fowler, Oreland, Marcusson, & Winblad, 1980; Saura, Kettler, Da Prada, & Richards, 1992). Based on dopamine metabolism rates, the prevalence of MAO-B to MAO-A activity in the striatum is 3:1 (Azzaro et al., 1985). MAO-A and MAO-B co-exist in the human brain, but they distribute in different brain areas on both regional and cellular levels. On the regional level, MAO-B is more active in the cortex, hippocampus, brain stem, and substantia nigra region. MAO-B activity has been reported in almost all brain regions except the cerebellum, occipital cortex and white matter, whereas, MAO-A activity has been reported to be active in the limbic regions of the nucleus accumbens, hypothalamus, mammilary complex, and the brain stem nuclei ( locus coeruleus and substantia nigra) (Westlund, Denney, Rose, & Abell, 1988; Kalaria, Mitchell, & Harik, 1988; Jossan, Gillberg, D'Argy, & Aquilonius, 1992; O'Carroll, Fowler, Phillips, Tobbia, & Tipton, 1983; Riederer & Youdim, 1986). On the cellular level, MAO-B has been found in serotonergic regions of the hypothalamus and in the astrocytes, whereas MAO-A is in the cell bodies of all catecholaminergic neurons and in the noradrenergic cell bodies of the locus coeruleus, sub-coeruleus complex, and the lateral
tegmentum. Additionally, MAO-A is the sole isozyme which has been found in neuronal cell bodies of the dopaminergic projections from the substantia nigra (Westlund et al., 1988; Moll, G., Moll, R., Riederer, Heinsen, & Denney, 1988; Konrodi et al., 1988; Konrodi et al., 1989; Riederer, Konradi, Hedensteit, & Youdim, 1989).

1.2. Smoking, MAO and Neurotransmission

Studies have shown similar inhibiting effects of smoking on both MAO-A and MAO-B activity in smoker’s brains. Using the PET technique, Fowler et al. (1996a, b) indicated that the inhibiting effect of cigarette smoking is 28% for MAO-A and 40% for MAO-B in the human brain. However, the degree of MAO-B inhibition in smokers is quite variable, ranging in one study from 17% to 67%, and in a subsequent study from 10% to 77%; the degree was unaffected by smoking duration or frequency (Fowler et al., 2000). MAO decrease rates vary by brain structure, ranging from 39% in the frontal cortex to 49% in the basal ganglia (Fowler et al., 1998). A single cigarette does not produce a measurable reduction in MAO-B in non-smokers, and the brain MAO-B activity in smokers remained at the same low level both 10 min and 11 hours later after smoking a cigarette (Fowler et al., 1999, 2000). This inhibition effect was not necessarily due to nicotine (Fowler et al., 1998). Adducts of 1,2,3,4-tetrahydroisoquinoline and 2-naphthylamine were suggested to be the inhibiting compounds in cigarette smoking (Mendez-Alvarez, Soto-Otero, Sanchez-Sellero, & Lopez-Rivadulla Lamas, 1997; Hauptman & Shih, 2001).

MAO-A activity was not measured in the current study. However, smoking inhibits both brain MAO-A and MAO-B, and sensory gating may be affected by changes in both. As such, neurotransmitters related to MAO-A or MAO-B are addressed in this chapter.
One of the primary roles of MAO-A and -B in the CNS is to regulate the monoamine neurotransmitters, including DA, NE, E, and 5-HT. The major endogenous substrates for MAO are divided into three categories: (1) the catecholamines, which includes dopamine (DA; Fahn, 1981), tyramine (T; Bianchine, 1985), epinephrine (E; Jenner, & Marsden, 1993), and norepinephrine (NE; Agid, Javoy, & Glowinski, 1973); (2) the aminoalkylindole 5-hydroxytryptamine (serotonin/5-HT; Duvoisin, 1981); (3) β-phenylethylamine (PEA; Calne & Langston, 1983), which is the only MAO-B selective neurotransmitter (Neff, Yang, & Goridiss, 1973). Furthermore, MAO-A preferentially deaminates norepinephrine (NE), serotonin (5-HT) and epinephrine (E), and MAO-B preferentially deaminates benzylamine and phenylethylamine (PEA). MAO-A and MAO-B equally catabolize dopamine (DA) and tyramine (for review, see Palmer, 1998).

Although MAO-A and MAO-B can equally catabolize DA, the metabolism of DA is predominately mediated by MAO-B in the human brain. MAO-B is responsible for 75% of DA metabolism in human brain homogenates (Garrick & Murphy, 1980; Azzaro et al., 1985). The metabolism of DA occurs mainly via the extraneuronal (glial) route by MAO-B (Oreland, Arai, & Stenstrom, 1983; Stenström, Hardy, & Oreland, 1987). MAO-A works on the metabolism of DA only when MAO-B is inhibited. MAO-A may also be responsible for some of the metabolism of DA which has been transported back into the neuronal cells (for review, see Palmer, 1998).

The metabolism of NE is predominately mediated by MAO-A upon re-uptake into neurons (Westlund, Denney, Kochersperger, Rose, & Abell, 1985; Westlund et al., 1988).
Serotonin (5-HT) metabolism in humans appears to be only MAO-A mediated. 5-HT is a selective MAO-A substrate. Serotonin cell bodies contain only MAO-B and not MAO-A; whereas in the nerve terminals, from which 5-HT is released and uptaken, only MAO-A is present (Fagervall & Ross, 1986; Kato, Dong, Ishii, & Kinemuchi, 1986; Butcher, Fairbrother, Kelly, & Arbuthnott, 1990).

Phenylethylamine (PEA) is the most selective MAO-B neurotransmitter in humans. The site of PEA metabolism is exclusively in the glial cells where the enzyme is localized (Patterson, Juorio, & Boulton, 1990).

2. Sensory Gating and Neurotransmitters

Schizophrenic patients show impaired ability to process sensory information, and sensory gating deficits have been found in schizophrenia. This deficit leads to disrupted auditory sensory gating as measured by the P50 paradigm. Control participants can reduce the amplitude of S2 by 80-90% of the amplitude of S1, whereas schizophrenics only reduce the amplitude of S2 by 10-20% (Freedman et al., 1983).

Neurotransmitter deficits have also been found in schizophrenia, affecting the catecholaminergic (Braff & Huey, 1988), serotonergic (Kapur & Remington, 1996), GABAergic (Roberts, 1972), glutamine/glutamate-ergic (Carlsson, Hansson, Waters, & Carlsson, 1999), and nicotinic/cholinergic systems. Some, but not all of these deficits may relate directly to sensory gating. However, because these neurotransmitters influence each other, the relationship between sensory gating and all these neurotransmitters will be discussed.

2.1. Catecholamine System and Sensory Gating
The catecholamines are amines derived from the amino acid tyrosine, and include the neurotransmitters epinephrine (E), norepinephrine (NE), and dopamine (DA). Drug studies with rats, healthy controls, and people with schizophrenia have yielded consistent findings on the relationship between catecholamines and sensory gating, as is described below.

Psychotic patients treated with neuroleptics (DA antagonists) showed improved function of sensory gating (Spohn, Lacoursiere, Thompson, & Coyne, 1977). Studies have also shown that catecholamine agonists can impair sensory gating in nonschizophrenic persons. These drugs effected temporary abnormal sensory gating, similar to deficits observed in schizophrenia (Braff & Huey, 1988). D-amphetamine and the agr2-adrenoceptor antagonist yohimbine, a drug that increases noradrenaline release, have been shown to impair P50 suppression in healthy individuals (Adler et al. 1994; Light et al. 1999). Furthermore, the DA agonist bromocriptine can also disrupt P50 suppression (Adler et al. 1994). A low dose of the NMDA antagonist ketamine has been found to fail to decrease P50 suppression (van Berckel et al. 1998).

In addition, neurophysiological deficits in auditory sensory gating, diminished hippocampal volume, and increased catecholamine metabolism in schizophrenics and their siblings have been reported (Waldo et al., 1994), suggesting that the sensory gating deficit is related to increased catecholamine metabolism.

Clinical studies have reported that amphetamine and phencyclidine can induce a psychosis that resembles schizophrenia (Bell 1965; Snyder 1973; Siegel 1978). Sensory gating can be disrupted both by amphetamine and phencyclidine (Adler et al. 1986;
Stevens et al., 1991). Amphetamines act as DA agonists by increasing DA release from nerve endings and by blocking DA reuptake. These combined effects rapidly increase DA concentrations in the synaptic cleft, promoting dopaminergic neurotransmission (from http://en.wikipedia.org). Similar drug-induced effects on sensory gating have been found in rats, at the level of behavior and single neurons (Swerdlow, Vaccarino, Amalric & Koob, 1986).

The contributions of $\alpha$- and $\beta$-adrenergic receptors and dopamine $D_1$- and $D_2$-receptors to sensory gating have been explored in an animal study in this regard (Stevens, Fuller, & Rose, 1991). In this study, the loss of N40 suppression in Sprague-Dawley rats depended on the noradrenergic and dopaminergic properties of amphetamine. Using a condition-test paradigm to measure sensory gating, control rats could suppress the response to the second of a pair of clicks. Amphetamine-treated rats fail to gate, which resembles the sensory gating deficit in schizophrenic humans. Furthermore, selective antagonists showed that both noradrenergic $\alpha$- and $\beta$-receptors and dopamine $D_1$-receptors contributed to sensory gating. Both the $\alpha$-antagonist (phentolamine) and the $\beta$-antagonist (timolol) administrated to amphetamine-treated rats could normalize gating by reducing the test response. The $D_1$-receptor antagonist (SCH 23390) normalized gating by enhancing the conditioning response. The $D_2$-receptor antagonist (sulpiride) did not significantly change amphetamine-induced gating deficit. Similar findings related to the $D_2$-receptor have been reported in humans (Oranje et al., 2004). Neither L-dopa nor bromocriptine (a $D_2$ agonist) reduced sensory gating in healthy volunteers. It was concluded that both noradrenergic $\alpha$- and $\beta$-receptors and dopamine
D₁-receptors contribute to sensory gating, but they may work in different ways. Noradrenergic and dopaminergic drugs were then suggested to act via different mechanisms and neuroanatomical loci because they normalized gating deficits in different ways.

2.2. Mesolimbic Dopamine System and Sensory Gating

There are four dopamine projections in the brain: mesocortical, mesolimbic, nigrostriatal and tuberoinfundibular pathways (Coffey & Cumming, 1994; Swartz, 1999). The mesocortical pathway projects from ventral tegmental area (VTA) to the frontal cortex, temporal cortex and anterior cingulum. The mesolimbic pathway projects from VTA to a variety of limbic structures, such as the nucleus accumbens, amygdale, hippocampus, and septal nuclei. The nigrostriatal pathway projects from the substantia nigra pars compacta to the striatum. The tuberoinfundibular pathways projects from the arcuate nucleus and the periventricular area of the hypothalamus to the infundibulum and the anterior pituitary gland where DA inhibits the release of prolactin.

Evidence has shown that the mesolimbic DA system has a major modulation effect on sensory gating. DA abnormalities have been found to contribute to sensory gating deficits observed in schizophrenics (Adler et al., 1998). DA agonists such as amphetamine and apomorphine disrupt sensory gating in normal participants and rats (Adler, Rose, & Freedman, 1986; Light et al., 1999). The DA receptor agonist bromocriptine also reduces P50 suppression in healthy humans (Adler et al., 1994). More directly, the D₂/D₃ agonist quinpirole, which selectively targets the mesolimbic DA receptors, significantly reduces hippocampal and cortical gating in rats. D₂ receptor
antagonist haloperidol pretreatment reverses this effect on cortical gating in rats (De Bruin, Ellenbroek, Van Luijtelaar, Cools, & Stevens, 2001).

The prefrontal cortex plays an important role in dopaminergic dysregulation. The noncompetitive NMDA antagonist ketamine has been found to elevate mesolimbic dopaminergic activity; the D₂ antagonist haloperidol decreases this activity (Breier et al., 1998; Jentsch, Tran, Taylor, & Roth, 1998). In a drug study, healthy male volunteers were administrated placebo-placebo, placebo-ketamine (0.3 mg/kg; intravenous), and haloperidol (2 mg; oral)-ketamine (0.3 mg/kg; intravenous) one week apart respectively (Oranje, Gispen-de Wied, Verbaten, & Kahm, 2002). Sensory gating was measured during these three conditions separately. Suppression of P50 in the placebo-ketamine condition did not differ from either the placebo-placebo or the haloperidol-ketamine condition; however, the combination of haloperidol and ketamine was found to disrupt P50 suppression. PET evidence shows that ketamine decreased striatal DA receptor availability in healthy volunteers and also increased striatal DA concentration (Breier et al., 1998). Furthermore, injection of ketamine directly into the prefrontal cortex of rats increased DA use in the nucleus accumbens, suggesting an involvement of the prefrontal cortex in the effect of NMDA antagonists (Jentsch et al., 1998).

In conclusion, the mesolimbic DA system appears to have a major modulating effect on sensory gating, and the disrupted P50 suppression found in schizophrenics relates to a reduced dopaminergic activity, most likely in the prefrontal cortex.

2.3. Serotonergic System and Sensory Gating

When the dopaminergic neurons are activated, serotonergic fiber has the effect on
dopaminergic neurons (Palfreyman et al., 1993). Studies found that serotonin is associated with the dopaminergic system and frontal lobe, which were the major pathogeny in schizophrenia (Kapur & Remington, 1996). Serotonin (5-HT) has also been found to be involved in some central function deficits, such as, depression, anxiety, impulsivity, and behavioral disorders in dementias (Robert, Aubin-Brunet, & Darcourt, 1999).

The roles of 5-HT receptors on sensory gating have been reported. Increased density of 5-HT$_{1A}$ receptors in the prefrontal and temporal cortices in schizophrenics has been reported (Hashimoto, 1993; Burnett et al., 1996). Postmortem studies in schizophrenics found that decreased 5-HT$_{2A/2C}$ binding in cortical areas, especially in the frontal cortex, compare to controls (Bennett et al., 1979; Burnett, Eastwood, & Harrison, 1996, Gurevich & Joyce, 1997). Ketanserin, a 5-HT$_{2A/2C}$ antagonist, disrupted the modulation of N40 suppression. Whereas, DOI, a 5-HT$_{2A/2C}$ agonist, has been reported to increase filtering and revert the reductions in filtering caused by ketanserin and amphetamine in rats (Johnson, Stevens, & Rose, 1998). 5-HT$_{2A/2C}$ agonists induce psychosis and 5-HT$_{2A/2C}$ antagonists obstruct psychosis (Robert et al., 1999).

Drug studies verified the role of 5-HT$_{3}$ receptor on sensory gating. First of all, serotonin receptor 5-HT$_{3}$ modulates the mesocortial and mesolimbic dopamine pathway (Hagan, Kilpatrick, & Tyers, 1993). Secondly, 5-HT$_{3}$ receptor may interact with $\alpha$7-nicotinic receptor. Tropisetron is a drug approved for clinical use outside the United States as an anti-emetic. It is a partial agonist at $\alpha$7 nicotinic receptors and an antagonist at 5-HT$_{3}$ receptors. It could improve deficits in P50 suppression in schizophrenic patients.
(Koike et al., 2005). Initially high P50 Test/Condition (T/C) ratios in patients were improved by administration of tropisetron. The improvement of P50 suppression by tropisetron has been suggested to be mediated via direct agonist effects on α7-nicotinic receptors and via effects on 5-HT3 receptors, the effects of the α7-nicotinic receptor stimulation and 5-HT3 antagonism may be synergistic. Animal studies found that the effect of tropisetron on deficient auditory gating is blocked by co-administration of the selective α7-nicotinic receptor antagonist methylycaconitine (Hashimoto, Iyo, Freedman, & Stevens, 2005), suggesting the role of α7-nicotinic receptors in the normalization of deficient sensory gating by tropisetron. However, tropisetron, like other 5-HT3 antagonists, increases release of acetylcholine (ACh) in the brain (Maura et al., 1992; Consolo, Bertorelli, Russi, Zambelli, & Ladinsky, 1994, Giovannini et al., 1998). Therefore, tropisetron’s stimulation of nicotinic receptors was suggested to be an indirect effect of 5-HT3 antagonism (Koike et al., 2005). Furthermore, Adler et al. (in press) have demonstrated that ondansetron, a highly selective 5-HT3 receptor antagonist, improves deficits of P50 suppression in schizophrenic patients.

2.4. GABAergic System and Sensory Gating

GABA is the main inhibitory neurotransmitter in the central nervous system. GABA dysfunction is believed to play a role in various neuropsychiatric disorders, especially in schizophrenia (Roberts, 1972; Benes & Berretta, 2001; Lara, 2002). Evidence from neurophysiologic and histopathological studies suggests an inhibitory deficit as a central pathophysiologic mechanism in schizophrenia. This deficit can be identified in sensory gating and paired-pulse studies, and may be related to decreases in inhibitory
interneurons found in schizophrenic patients (Freedman, Adam, & Leonard, 2000; Benes & Berretta, 2001; Daskalakis et al., 2002).

PET studies have found increased basal metabolism in the hippocampal formation of schizophrenics (Heckers et al., 1998). The GABA system in this region may be dysfunctional in schizophrenia (Benes, 1999; Benes & Berretta, 2000). It was suggested that decreased GABAergic transmission in specific cortical areas could result in rearrangement, and possibly enlargement, of sensory, memory and cognitive areas among schizophrenics (Benes & Berretta, 2001).

In an animal study, GABA-B antagonists have been found to inhibit suppression of P50 amplitude from 75% to 45% (Hershman, Freedman, & Bickford, 1995). It has been suggested that S1 evokes the α7-nicotinic receptors of inhibitory interneurons, resulting in the release of GABA, which in turn activates GABA-B receptors and decreases glutamate release, which then diminishes the S2 response (Adler et al., 1998).

2.5. Glutamine/Glutamate System and Sensory Gating

Glutamatergic models have implied a role of the anterior cingulate and other parts of the limbic system in the pathophysiology of schizophrenia (Carlsson, Hansson, Waters, & Carlsson, 1999). Using in vivo short-echo-time 1H magnetic resonance spectroscopy (MRS), glutamine levels were found to be significantly higher in the left anterior cingulate and thalamus of the nerve-treated patients with schizophrenics than in the healthy humans (Theberge et al., 2002). No other metabolite differences were found between the two groups. Most of the physiologically active glutamate is derived from glutamine, and then is taken up by astrocytes, transported back to the presynaptic neuron, and
reconverted to glutamate (Rothman et al., 1999). The higher levels of glutamine indicate less glutamatergic activity if there was an abnormality in the conversion of glutamine to glutamate (Theberge, et al, 2002).

Glutamate facilitates striatal DA release (DiChiara & Morelli, 1993). Dopamine may presynaptically inhibit striatal glutamate release via D₂ receptors located on the corticostriatal neuron terminals (Carlsson & Carlsson, 1990). NMDA receptor blockade reduces basal ACh release and also prevents D₁-dependent stimulation of ACh release (Damsma, Robertson, Tham, & Fibiger, 1991).

No direct relationship between glutamine/glutamate and P50 sensory gating can be found from previous studies. A rat study examined the functional role of striatal metabotropic glutamate receptors (mGluRs) on prepulse inhibition (PPI), an acoustic startle response measure. The results verify a role of mGluRs in the nucleus accumbens in the regulation of PPI. PPI has been reported to be abnormal in Huntington's and schizophrenia. The study suggested that mGluRs may have potential as novel therapeutic targets for these diseases (Grauer & Marquis, 1999). Because PPI is one type of sensory gating measurement, the role of mGluRs on PPI indicates that glutamine/glutamate may also relate to the P50 sensory gating.

2.6. Nicotinic Cholinergic System and Sensory Gating

Sensory gating deficit is proposed to be associated with decreased function and/or expression of the α7-nicotinic acetylcholine receptor (α7-nAChR). Hippocampal neurons can rapidly inhibit the response to repeated sensory stimulation, and the inhibitory function has been linked to the α7-nAChR subunit (Luntz-Leybman, Bickford, &
Freedman, 1992). Many hippocampal interneurons are depolarized by activation of the α7-nicotinic receptor subunit. α-bungarotoxin, a type of antagonist of α7-nicotinic receptor, labels the GABA-containing interneurons in all regions of the hippocampus (Adam, 1999). A genetic study found that the chromosome I5q14 locus of the α7-nAChR gene was associated with P50 sensory gating abnormalities (Freedman et al., 2003).

A recent drug study further verified that α7-nicotinic acetylcholine interacts with GABAergic neurotransmission and influences sensory gating (Hajo et al., 2005). N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide hydrochloride (PNU-282987) is a novel selective agonist of the α7-nAChR. It can evoke whole cell currents from cultured rat hippocampal neurons that are sensitive to the selective α7-nAChR antagonist methyllycaconitine and so enhance GABAergic synaptic activity. In anesthetized rats, systemic administration of PNU-282987 could restore the P50 sensory gating deficit in the hippocampal CA3 region induced by amphetamine. Furthermore, PNU-282987 improved the hippocampal gating deficit in some anesthetized rats, and enhanced amphetamine-induced hippocampal oscillation. This finding suggests that the α7-nAChR agonist PNU-282987 improves auditory gating and hippocampal oscillation by enhancing hippocampal GABAergic neurotransmission.

3. Conclusion

Neurotransmitters related to MAO and sensory gating have been discussed here at length. It is clear that catecholamines play an important role in sensory gating. For example, studies have shown that catecholamine agonists impair sensory gating function among normal humans. These drugs effect a temporarily abnormal sensory
gating that is similar to the sensory gating deficits observed in schizophrenics (Braff & Huey, 1988). The contributions of α- and β-adrenergic receptors and dopamine D₁- and D₂-receptors to sensory gating have been explored. Both noradrenergic α- and β-receptors and dopamine D₁-receptors contribute to sensory gating, but they may work on sensory gating in different ways. D₂-receptors may not contribute to sensory gating.

The role of 5-HT₂ and 5-HT₃ receptors on sensory gating has been reported. The 5-HT₂A/2C antagonist and 5-HT₃ receptor antagonist could improve deficits in P50 suppression in schizophrenic patients. However, the 5-HT₃ antagonists may increase release of acetylcholine (ACh) in the brain. Therefore, the effect of 5-HT₃ receptor antagonist on sensory gating was suggested to be an indirect stimulation of nicotinic receptors by 5-HT₃ antagonism. Serotonin receptor 5-HT₃ modulates the mesocortial and mesolimbic dopamine pathway. When the dopaminergic neurons are activated, serotonergic fiber has the effect on dopaminergic neurons. Therefore, 5-HT plays a role in sensory gating. However, because it also interacts with nicotinic cholinergic system and dopamine system, it may play both direct and indirect effects on sensory gating.

Administration of GABA-B antagonists could inhibit suppression of P50 amplitude from 75% to 45% in a study. It has been suggested that the first stimulus evokes the α7-nicotinic receptors of inhibitory interneurons, and results in the release of GABA, which in turn activates GABA-B receptors and decrease glutamate release, and then diminishes the response to the second stimulus. Therefore, GABA influences sensory gating through the α7-nicotinic receptors. GABAergic system and nicotinic system interact with each other.
No direct relationship between glutamine/glutamate and P50 sensory gating can be found. However, the functional role of striatal metabotropic glutamate receptors (mGluRs) on prepulse inhibition (PPI) has been verified. The role of glutamine/glutamate on sensory gating was then suggested. Glutamate also interact with DA, it facilitates striatal DA release. Dopamine may presynaptically inhibit striatal glutamate release via D2 receptors located on the corticostriatal neuron terminals. NMDA receptor blockade reduces basal ACh release and also prevents D1-dependent stimulation of ACh release.

The role of α7-nicotinic acetylcholine receptor (α7-nAChR) on sensory gating has been verified. A recent genetic study found that the chromosome l5q14 locus of the α7-nAChR gene was associated with the P50 sensory gating abnormalities. The α7-nicotinic acetylcholine interacts with GABAergic neurotransmission and then influences sensory gating.

In the present study, a positive relationship between MAO and sensory gating was found. However, no direct evidence can be found to support this finding. Exploration on neurotransmitters shows that sensory gating is modulated by activities in the catecholaminergic system, serotonergic system, GABAergic system, and nicotinic cholinergic system. Dysfunction of these neurotransmitters systems will result in an abnormal sensory gating. These neurotransmitters systems also interact with each other and work on the sensory gating at the same time. The metabolism of the neurotransmitter DA is predominately mediated by MAO-B. The metabolism of the neurotransmitter NE is predominately mediated by MAO-A. Serotonin (5-HT) metabolism
in humans appears to be only MAO-A mediated. Therefore, MAO may influence the DA, NE, and 5-HT activity, which in turn affects sensory gating function.

4. Future Work

The relationship between sensory gating and MAO was found in the study. Further verification of the relationship is needed. This work can be conducted in different human samples, such as schizophrenics, normal people. Furthermore, comparing sensory gating and MAO between males and females, or between young and old participants will help to explore the roles of gender and age on MAO and sensory gating.

Dose-dependent decrease of MAO among smokers have been reported before, this study do not support the conclusion directly. However, CO level was found to be negatively correlate with MAO level in the study. Further verification on dose-dependent MAO decrease among smokers is suggested.

Because sensory gating is influenced by neurotransmitters in the brain, brain MAO activity, and neurotransmitters activities are suggested to be measured in the future work. Discussion on neurotransmitters, sensory gating and MAO rises some questions, such as how MAO adjusts the neurotransmitters in the brain and how MAO level is adjusted in the human brain. These questions need to be answered in the future.
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Figure 2: Compare CO Level between Low and High Dependent Smokers
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Appendixes

Appendix A: Adult/Primary Caregiver Consent Form

Title: Biopsychosocial Characteristics of Teenagers Who Do and Do not Smoke
Investigator: Helen J. Crawford, Ph.D.
Professor of Psychology
Virginia Tech

1. PURPOSE OF THE PROJECT

Many teenagers smoke, but we do not understand well why they smoke and now it affects their attentional and information processing abilities. This project will help us identify biopsychosocial characteristics of male and female teenagers, aged 13 to 17, who do and do not smoke cigarettes. We have conducted similar research with young adults aged 18 and older.

This project will involve your teenager coming to Virginia Tech in Blacksburg for a 2-3 hour research session in the psychology department. He/she will fill out questionnaires and have his/her brain wave activity recorded while doing simple visual and auditory tasks. Finally, if he/she consents, a small amount of blood will be drawn by a phlebotomist to assess for an enzyme that is found to be lower in adult smokers than non-smokers. Your teenager will NOT smoke a cigarette during this project.

This project is supported by the Virginia Youth Tobacco Project Coalition through a grant to Helen Crawford and other Virginia Tech faculty. The proposed research has been approved by the university’s human subjects committees.

To compensate your teenager for participation, he/she will be given $25. As you evaluate this project, please feel free to call Dr. Crawford (231-6520 days; 961-4279 evenings until 9 PM) to discuss it further.

2. PROCEDURE TO BE FOLLOWED IN THE STUDY

To verify that your teenager qualifies, we would appreciate your filling out the enclosed medical questionnaire and returning it to Dr. Crawford in the enclosed stamped envelop, along with the signed consent form (this one) and the signed assent form from your teenager.

It will be kept confidential and not shared with anyone. Specifically, if your teenager has or has had any neurological or medical problems (e.g., seizure, epilepsy, tumor, cancer, diabetes, blood disorder, schizophrenia or other major mental problem) we will not ask them to participate. If your teenager smokes, we are looking for those who have for at least 6 months and who smoke 5 or more cigarettes on the average per day. If your teenager does not smoke, we are looking for those who have at most experimentally tried
Teenage Smoking Project

Upon arrival at the laboratory (Room 254, Williams Hall, Virginia Tech), your teenager will be shown the questionnaires and the experimental set-up. You are welcome to be with them at this time. Only after all questions are answered will your teenager sign again the assent form indicating a willingness to participate. Once the experiment begins, he/she can withdraw participation at anytime during the research and still be paid $25.

This experiment takes between 2 and 3 hours. Each part is described below.

Part 1: All teenagers will be tested for tobacco intake indirectly with a Micro-Smokelyzer CO monitoring device; smokers show more CO in their breath. Next they will be given two paper strips (control and phenylthiocarbamide (PTC)) to touch to their tongue and describe what they experienced. Some individuals taste something whereas others do not. This will take 5 minutes.

Part 2: We are interested in learning more about individual differences in teenagers who do and do not smoke. We hope this information will contribute to our understanding of why some people start smoking cigarettes. We will ask your teenager to fill out several questionnaires that will ask him/her about their smoking habits, handedness, and their attentional and personality styles. This will take 20 - 40 minutes.

Part 3: We are interested in how your teenager performs several attentional tasks while having his brain wave activity recorded. He/she will wear an EEG cap, which is like a swimming cap with several buttons built into it. These are electrodes that measure brain activity. They merely measure EEG, they do not produce any electricity. We will also place small electrodes on their face to measure eye blinks. To protect from infection, the cap and electrodes will have been disinfected by the experimenter prior to your arrival. An elastic band around the chest helps hold the cap tightly on your head. This may be slightly uncomfortable. If so, we can adjust it. In the process of putting cap on, the skin will be cleaned with a mildly abrasive cleanser. If your teenager has skin allergies, we will only use alcohol as a cleanser. The experimenter has thoroughly sanitized the electrodes and washed the electrode cap. The experimenter will wear clean rubber gloves while attaching the electrodes.

They will sit in a room, much like a hearing test booth. There will be a computer screen in front of them, and a speaker behind their head. We will be recording their brain waves during rest with eyes open and closed and during three tasks. Auditory tones will be presented from a loudspeaker behind their head and they will be asked to count the number of pairs of tones there are. Visual stimuli (colors, words) will be presented on a monitor and your teenager will press a response key to give answers as to the color of the stimulus or whether it was present before or not. They will also do several other tasks including identifying emotions of faces, and pushing a button as to whether an arrow points left or right. This takes about 40 minutes.

Part 4: If you and your teenager agree, a licensed phlebotomist [Janet Rinehart, Laboratory Specialist Senior, Human Nutrition, Foods and Exercise] will draw a small
amount (20 ml, equivalent to a couple of teaspoons) of blood from the arm with a needle for blood chemistry analysis. It takes about 10 minutes and will occur in Wallace 238 on the Virginia Tech campus. At no time will a name be associated with the blood assays; only a subject number.

This blood will be frozen for a study of Monoamine Oxidase, an enzyme involved in the production of the neurotransmitter dopamine, differences in teenage smokers and nonsmokers. We have found that adult smokers have less monoamine oxidase, and now we wish to know if teenage smokers do too. Professor Neal Castagnoli, VT chemistry department and his colleagues, will analyze your blood for the level of blood platelets and the level MAO in it. The amount of MAO activity will also be correlated with EEG activity recorded. If your teenager is phobic or highly fearful of needles or blood, they will not participate.

3. ANONYMITY OF SUBJECTS AND CONFIDENTIALITY OF RESULTS

The information your child shares with the researchers will only be available to other individuals working on the project. Further, all questionnaires and physiological data will be identified only with a number so that it does not identify your teenager by name. The information will be kept in a locked office, and all of the information will be kept strictly confidential.

4. RISKS AND DISCOMFORTS

There are minimal risks from participation in this study. It is important for you to know that your teenager does not have to answer any questions that he/she does not want to, and that he or she can stop at any time. The strip of paper may taste bitter, and if so, a candy will be given afterwards. The EEG cap may be a little uncomfortable; if so, we will adjust it to make them more comfortable. The EEG device is constructed in such a way that no electricity can come from it to them.

Potential risks involved drawing of the blood is minimal. Your teenager has had blood drawn before and knows what it is like. They may feel some discomfort from the needle. If he/she is phobic or highly fearful of needles or blood, they should not participate. When the blood (about two teaspoons) is drawn, every precaution is taken to make them feel comfortable. Occasionally, a bruise may result from a blood draw with no known detrimental effect to the health of the participant. The medical laboratory technologist responsible for taking the blood samples is certified by the American Society of Clinical Pathologists. A special chair is available to participants for their comfort. Participants will be allowed to rest after the blood draw and will be served with orange juice if they want. All the personnel involved with analyzing the blood have undergone training in the Guidelines for Bloodborne Pathogen Exposure Control administered by the Environmental Health and Safety Services of the Occupational Health Lab Safety Division at Virginia Tech. Universal precautions will be taken such as use of gloves when handling blood samples. If anyone is exposed to the blood, we have the right to test your
blood or anyone exposed to your body fluids for HIV, as required by university policy, and you (parent/guardian) will be informed of the results of such a test.

5. EXPECTED BENEFITS

No guarantees or promises are being made to you or your teenager. His/her participation will help advance knowledge of why some teenagers smoke and others do not.

6. FREEDOM TO WITHDRAW

Your teenager and you have the freedom to withdraw from participation at any time. Your teenager does not have to answer any questions that he/she desires not to. After the experiment starts, if your teenager decides not to continue participation, he/she will still be paid.

7. USE OF RESEARCH DATA

The information from this project may be used for scientific or educational purposes. It may be presented at scientific meetings and/or published and reproduced in professional journals, books, or used for any other purpose that Virginia Tech's Department of Psychology considers proper in the interest of education, knowledge, or research. However, information collected will not be presented in any manner that will identify your teenager by name.

8. PARTICIPANT CONSENT

I have read the purpose of this project. If wanted, I have had a chance to ask questions and have them answered by calling Dr. Crawford at (540) 231-6520 or 961-4279. I have verified that my teenager would like to participate in the research, with knowledge that he/she may withdraw at any time. I understand that he/she may stop answering questions, interrupt the procedure or withdraw from the study at any time. I voluntarily consent for my child to be a participant in this study. I have filled out the accompanying medical questionnaire, and to my knowledge I know of no reason why my teenager should not participate. At the time of my teenager's participation, I will verify that they are not taking any medications that could interfere with the experiment (e.g. on an antibiotic or antihistamine). I understand that the information collected will be combined with information from other individuals for purposes of data analysis, and that neither I nor my teenager will be identified by name in any way. I further understand that if I have any questions about this research and its conduct, I will contact one of the following:

Investigator: Helen Crawford, Ph.D. Phone: 540-231-6520
Psychology Department Human Subjects Committee:
   David Harrison, Ph.D. Phone: 540-231-4422
Virginia Tech Institutional Review Board:
   David M. Moore, Ph.D Phone: 540-231-4991
My teenager may participate in the blood draw. Yes  No
I agree to my teenager’s participation in the described study.

____________________________________________________________________
Signature of Parent or Guardian                                                  Date Signed
Please clearly print name of the above signature: ________________________________
Address: ____________________________  ____________________________
Phone #: Home: ______________________  Work: ____________________________
Please print name of your teenager: ____________________________________________

Please keep one copy of this consent form.
Appendix B: Teenager’s Assent Form

Title: Biopsychosocial Characteristics of Teenagers Who Do and Do not Smoke
Investigator: Helen J. Crawford, Ph.D.
Professor of Psychology
Virginia Tech

1. PURPOSE OF THE PROJECT

We are studying teenagers who either smoke or do not smoke. Many teenagers smoke, but we do not understand well why they smoke or how it affects their attention and information processing abilities. This project will help us identify common characteristics (attentional and personality styles, brain wave activity, taste preferences) of male and female teenagers, aged 13-17, who do and do not smoke cigarettes. We have conducted similar research with young adults aged 18 and older.

Please discuss this project with your parent/guardian. If you would like to discuss it with us, please call Dr. Crawford at 231-6520 (evenings before 9 PM: 961-4279).

You will come to Virginia Tech in Blacksburg for a 2-3 hour research session in the psychology department. You will fill out questionnaires and have your brain wave activity recorded while doing simple visual and auditory tasks. Finally, if you are not phobic, a small amount of blood will be drawn by a licensed technician at Virginia Tech to assess for an enzyme that is found to be lower in adult smokers than non-smokers. You will NOT smoke a cigarette during this project. For your time, you will be given $25.

This project is supported by the Virginia Youth Tobacco Project Coalition through a grant to Helen Crawford and other Virginia Tech faculty. The proposed research has been approved by the university’s human subjects committees.

2. PROCEDURE TO BE FOLLOWED IN THE STUDY

It is important that you understand what will be done in the experiment. Please read this and discuss it with your parent/guardian. If there are any words you do not understand, please ask your parent/guardian. If you have any questions, please call Dr. Crawford.

First, your parent/guardian will fill out a medical questionnaire to make sure you qualify. Your parent will sign a consent form and send it to Dr. Crawford, along with the medical questionnaire and this assent form. If you have had any major medical problems (e.g., diabetes, blood disorders, seizure, epilepsy, tumor, cancer, schizophrenia, or other major mental problem), we will not ask you to participate.

For the teenager who smokes, we are looking for those who have for at least 6 months and who smoke 5 or more cigarettes on the average per day. For the teenager who does not smoke, we are looking for those who have at most experimentally tried it.
Upon arrival at the laboratory, you will be shown the questionnaires and the experimental setup. You will sign the assent form again. Once the experiment begins, you can withdraw participation at anytime during the research and still be paid $25. This experiment takes between 2 and 3 hours. Each part is described below.

Part 1: First we will ask you to blow into a tube to measure your carbon monoxide level in your breath. Smokers have more CO in their breath. Next, you will be given two paper strips touch to your tongue and describe what you experienced. Some individuals taste something whereas others do not. Afterwards, we will give you a candy if you want. This will take 5 minutes.

Part 2: Next you will fill out several questionnaires that will ask you about your smoking habits, handedness, and attentional and personality styles. This will take 20 - 40 minutes. You can skip any questions you want to.

Part 3: Next, you will perform several simple tasks while having your brain wave activity recorded. You will wear an EEG cap, which is like a swimming cap with several buttons built into it. These are electrodes that measure your brain activity. They only measure EEG; they do not produce any electricity. We will also place small electrodes on your face to measure eye blinks. An elastic band around the chest helps hold the cap tightly on your head. This may be slightly uncomfortable. If so, we can adjust it. In the process of putting the cap on, the skin will be cleaned. If you have skin allergies, we will only use alcohol as a cleanser. The experimenter has thoroughly cleaned the electrodes and washed the electrode cap. The experimenter will wear clean rubber gloves while attaching the electrodes.

You will sit in a room, much like a hearing test booth. There will be a computer screen in front of you, and a speaker behind your head. We will be recording your brain waves during rest with eyes open and closed and during three tasks. Each task takes about five minutes. Auditory tones will be presented from a loudspeaker behind your head and you will be asked to count the number of pairs of tones there are. Visual stimuli (colors, words) will be presented on a monitor and you will press a response key to give answers as to the color of the stimulus or whether it was present before or not. They will also do several other tasks including identifying emotions of faces, and pushing a button as to whether an arrow points left or right. This takes about 40 minutes.

Part 4: If you and your parent agree, a licensed technician will draw a small amount (20 ml, equivalent to a couple of teaspoons) of blood from your arm. It takes about 5 minutes. At no time will your name be associated with the blood; only a subject number. This blood will be frozen for a study of Monoamine Oxidase, an enzyme that is found less in adult smokers. We want to know if there are differences in teenage smokers and non-smokers.

3. ANONYMITY OF SUBJECTS AND CONFIDENTIALITY OF RESULT
The information you share with the researchers will only be available to other individuals working on the project. Your parents will not be told about your responses. Your information will only be identified with a subject number and kept secret. The information will be kept in a locked office.

4. RISKS AND DISCOMFORTS

The strip of paper may taste bitter, and if so, a candy will be given. The EEG cap may be a little uncomfortable; if so, we will adjust it to make them more comfortable. The EEG device is constructed in such a way that no electricity can come from it to them. You have had your blood drawn before and know what it is like. You may feel some discomfort from the needle.

5. EXPECTED BENEFITS

No promises are being made to you or your parent. You will help us understand why some teenagers smoke.

6. FREEDOM TO WITHDRAW

You have the right to stop participating at any time. You do not have to answer any questions that you do not want to. After the experiment starts, if you decide not to continue, you will still be paid.

7. USE OF RESEARCH DATA

The information from this project may be used for scientific or educational purposes. Your name will not be used.

8. COMPENSATION

For your participation in this study, you will be given $25 whether you complete the study or not.

9. PARTICIPANT ASSENT

If you want to be in the study, please sign this form to let us know that you understand what the study is about, you know who to ask if you have any questions, and that you understand that you can stop at any time. If I have questions, I can call the following people.

Investigator: Helen Crawford, Ph.D. Phone: 540-231-6520
Psychology Department Human Subjects Chair:
    David Harrison, Ph.D. Phone: 540-231-4422
Virginia Tech Institutional Review Board Chair:
David Moore, D.V.M.                                Phone: 540-231-4991

I am willing to have about two teaspoons of blood drawn from my arm. Yes No
I would like to participate.

_____________________________________________________________________
Your signature       Date Signed
_____________________________________________________________________
When in the experiment, we will ask you to sign again:

_____________________________________________________________________
Your signature       Date Signed

Print your name: __________________________________
What is your age? _________________________________
Do you smoke or not?   I smoke.     I do not smoke.

Please keep one copy of this consent form.
Appendix C: Medical Screening Questionnaire

In order to verify that you are qualified for the study, please answer the following questions. The following information is required by the Institutional Review Board to screen for possible participation in EEG studies. We must know if your teenager had any medical problems that might keep him/her from participating. This will be completely confidential. Upon receipt, the name will be removed and a subject number will be given to this questionnaire.

1. Since birth has he/she ever had any major medical problems? Yes  No If yes, please explain.
2. Since birth has he/she ever been hospitalized? Yes  No  If yes, please explain.
3. Has he/she ever hit the head and lost consciousness? Yes  No  If yes, please explain.
4. Did he/she ever have problems where a counselor, psychologist or psychiatrist was seen? Yes  No  If yes, please explain.
5. Does he/she use tobacco (smoke, chew)? Yes  No  If yes, please explain.
6. Does he/she any hearing problems? Yes  No  If yes, please explain.
7. Does he/she currently have or have you ever had any of the following? Circle yes or no.
   arthritis
   asthma
   lung problems
   heart problems/disease
   diabetes
   hypoglycemia
   hypertension
   low or high blood pressure
   hepatitis
   neurological problems
   epilepsy or seizures
   brain disorder
   stroke
   cancer
If you have circled yes to any of the above conditions, please explain.
8. Does he/she ever been diagnosed formally to have had:
   learning deficiency or disorder
   reading deficiency or disorder
   attention deficit disorder
   attention deficit hyperactivity disorder
9. Do you have a high fear of needles or blood? Yes  No
10. List any over-the-counter or prescription medications presently being taken.
11. Do he/she have or had any other medical conditions that you can think of? If yes, please note them below.
Appendix D: Fagerström Test for Nicotine Dependence

Type of Cigarette Smoked: ____________________________

1. How soon after you wake up do you smoke your first cigarette?
   Within 5 minutes (3 points) ___
   6 – 30 minutes (2 points) ___
   31-60 minutes (1 point) ___
   After 60 minutes (0 point) ___

2. Do you find if difficult to refrain from smoking in places where
   It is forbidden e.g. in church, at library, cinema, etc?
   Yes (1 point) ___
   No (0 point) ___

3. Which cigarette would you hate most to give up?
   The first one in the morning (1 point) ___
   All others (0 point) ___

4. How many cigarettes/day do you smoke?
   10 or less (0 point) ___
   11-20 (1 point) ___
   21-30 (2 points) ___
   31 or more (3 points) ___

5. Do you smoke more frequently during the first hours after waking than during the rest
   of the day?
   Yes (1 point) ___
   No (0 point) ___

6. Do you smoke if you are so ill that you are in bed most of the day?
   Yes (1 point) ___
   No (0 point) ___

TOTAL: __________
Appendix E: Tobacco Use History and Patterns Questionnaire

CHOICES

Smoking History & Patterns Questionnaire

The next several questions will be asking you how old you were when different things began to happen to you. You will be asked to respond with your age at this time in number of years and months. For example if you had just turned 12 when this happened then the correct response would be 12 years and 0 months, if instead you were 12 and a half you would answer with 12 years and 6 months.

1. How old were you when you first smoked a whole cigarette?
   _____ ___ years _________ months (Range = 05 yrs. 00 mos. to 19 yrs. 11 mos.)

2. How old were you when you smoked at least 100 cigarettes (100 cigs = 5 packs)?
   _____ ___ years _________ months (Range = 05 yrs. 00 mos. to 19 yrs. 11 mos.)

3. How old were you when you started weekly cigarette smoking (at least 2 days/week for 4 consecutive weeks)?
   _____ ___ years _________ months (Range = 05 yrs. 00 mos. to 19 yrs. 11 mos.)

4. Were you ever a daily smoker, that is smoked at least 1 cigarette per day for 30 consecutive days?
   0) No
   1) Yes (Go to #7)

5. Since you started weekly smoking, how many times have you tried to quit smoking?
   _________ # times (if 00, go to #15) (Range = 00 to 99)

6. What is the longest time you were able to stay of cigarettes during a quit attempt?
   _________ days off cigarettes (Go to #11) (Range = 001 to 999)

7. How old were you when you started daily cigarette smoking (1 cigarette/day for 30 days)?
   _____ ___ years _________ months (Range = 05 yrs. 00 mos. to 19 yrs. 11 mos.)

8. Since you started daily smoking, how many times have you tried to quit smoking?
   _________ # times (if 00, go to #15) (Range = 00 to 99)

9. Since you began daily smoking, how many times did you try to quit where you were able to stay off cigarettes for 24 hours or more?
   _________ # times (if 00, go to #15) (Range = 00 to 99)

10. Since you started daily smoking, what is the longest time you were able to stay off cigarettes during a quit attempt?
    _________ days off cigarettes (Range = 001 to 999)
11. Have you made a serious quit attempt (intentional, lasted at least 24 hours) in the past month?
   0) No
   1) Yes (Go to #13)

12. Have you made a serious quit attempt (intentional, lasted at least 24 hours) in the past 6 months?
   0) No
   1) Yes

13. What were your reasons for wanting to quit smoking cigarettes? (mark all that apply)
   ___ Pressure from friends/boyfriend/girlfriend
   ___ Current health concerns (coughing, sore throat)
   ___ Pressure from parents
   ___ Nasty habit (bad breath, clothes smell)
   ___ Too expensive
   ___ Pregnant
   ___ Future health concerns
   ___ Concern about effect on others

14. Mark any method you have used to help you in an attempt to quit smoking. (mark all that apply)
   ___ Willpower/Cold turkey (just quit)
   ___ Gradual reduction (cut back a little at a time)
   ___ Stop smoking program
   ___ Use nicotine patch
   ___ Quit with friends, relatives, etc
   ___ Use nicotine gum
   ___ Zyban or other medications to help quit

15. Do you think you will be smoking 5 years from now?
   0) No
   1) Yes

16. How do you get your cigarettes? (mark all that apply)
   ___ I buy them myself
   ___ My friends buy them for me
   ___ My parents buy them for me
   ___ My brother(s)/sister(s) buy them for me
   ___ Others buy them for me
   ___ I get them off of other people (friends, parents, siblings)
   ___ I steal them

17. How do you get most of your cigarettes?
   1) I buy them myself
   2) My friends buy them for me
   3) My parents buy them for me
   4) My brother(s)/sister(s) buy them for me
   5) Others buy them for me
   6) I get them off of other people (friends, parents, siblings)
   7) I steal them
18. On how many days out of the last 30 did you use chewing tobacco like RedMan, Levi Garrett, Beechnut?

_________ # days (Range = 00 to 30)

19. On how many days out of the last 30 did you use snuff such as Skoal, Skoal Bandits, or Copenhagen?

_________ # days (Range = 00 to 30)

20. On how many days out of the last 30 did you smoke cigars? (includes small cigars)

_________ # days (Range = 00 to 30)

21. On how many days out of the last 30 did you smoke clove cigarettes?

_________ # days (Range = 00 to 30)

22. On how many days out of the last 30 did you smoke bidi’s?

_________ # days (Range = 00 to 30)

23. How likely is it that you will be a non-smoker one year from now?

1) Not at all likely
2) A little likely
3) Somewhat likely
4) Pretty likely
5) Very likely

24. How much would you like to quit smoking?

1) Not at all
2) A little
3) Somewhat
4) Pretty much
5) Very much

25. If you try to quit smoking in the next month, how successful do you think you would be?

1) Not at all successful
2) A little bit successful
3) Somewhat successful
4) Quite successful
5) Very successful

26. If you try to cut down on your smoking in the next month, how successful do you think you would be?

1) Not at all successful
2) A little bit successful
3) Somewhat successful
4) Quite successful
5) Very successful
Appendix F: Differential Attention Processes Inventory

This questionnaire is an assessment of individual differences in the abilities to selectively attend and to carry out several tasks simultaneously. These abilities are NOT related to general intelligence. Describe your experiences in terms of frequency, where Never=0 and where Always=6.

1. Can you concentrate on reading or studying while in a noisy room?
2. Can you get so involved in an activity that you don’t have extraneous thoughts (don’t think about other things)?
3. Can you block out advertising commercials on TV or radio?
4. Have you ever had the experience of not hearing or not remembering what a person said to you while you are involved in an activity and yet found yourself acting upon that person’s statement at a later time?
5. Can you lose yourself in thought so that you are hardly aware of the passage of time?
6. Can you ignore or reduce pain (without drugs) if you want to?
7. Can you ignore music when you are reading or studying?
8. Can you shift your attention away from bothersome noises or distractions in a room so that they no longer bother you?
9. Can you concentrate easily on reading or studying when music is playing in the same room?
10. Can you lose yourself easily in thought?
11. Can you doodle at the same time that you are having a conversation with another person?
12. Can you attend to music easily and not hear conversations going on nearby in the same room?
13. When you are at a party, can you attend to one conversation and ignore another one which is close by and audible?
14. Do you ever miss or arrive late for appointments or class because you were so involved in something that you forgot the time?
15. Can you drift off into your own thoughts or daydreams and still attend to someone else’s conversation at the same time?
16. Can you write easily while at the same time listen to a conversation?
17. Can you wander off into your own thoughts while doing an activity so that you actually forget what you were doing, and then find a few minutes later that you have finished the job without even being aware of having finished it?
18. Can you daydream so deeply that you do not hear someone talking to you?
19. Can you be so involved in reading or studying that when someone talks to you, you do not hear them?
20. If you want to take a nap, can you easily ignore others conversing in the same room?
21. Can you write easily while at the same time listen to the radio or TV?
22. Can you be so involved in reading or studying that when someone talks to you, you do not hear the at the time yet later realize that they have spoken to you?
23. Can you be so involved in dancing that you are almost not aware of your surroundings?
24. Can you carry out a moderately complex activity at the same time that you are having a conversation with another person?
25. Can you talk on the telephone while doing some other physical activity?
26. Can you read or study easily while at the same time listen easily to a conversation?
27. Can you read or study easily while at the same time listen to the talking of the radio or TV?
28. Can you read or study easily while at the same time listen to music?
29. Can you write easily while at the same time listen to music?
30. Can you carry out a physical activity easily while listening to a conversation?
31. Can you carry out a physical activity easily while listening to someone talking on radio or TV?
32. Can you carry out a physical activity easily while listening to music?
33. Can you wake up at night at some predetermined time during the night? (e.g., know you have to wake up at 4 AM and do so without any external help, such as an alarm clock)
34. Can you read or study easily while actively involve in conversation?
35. Can you listen to a conversation, be writing or studying at the same time, and also carry on some other internal thoughts unrelated to the first two at the same time?
36. Can you carry out a physical activity easily while listening to someone talking on radio or TV?
37. Can you carry out a physical activity easily while listening to music?
38. Can you wake up at night at some predetermined time during the night? (e.g., know you have to wake up at 4 AM and do so without any external help, such as an alarm clock)
39. Can you read or study easily while actively involve in conversation?
40. Can you listen to a conversation, be writing or studying at the same time, and also carry on some other internal thoughts unrelated to the first two at the same time?
Appendix G: Cognitive Failures Questionnaire

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the last six months. Please indicate frequency where Never=0 and where Always=4.

1. Do you read something and find you have not been thinking about it and must read it again?
2. Do you find you forget why you went from one part of the house to the other?
3. Do you fail to notice signposts on the road?
4. Do you find you confuse right and left when giving directions?
5. Do you bump into people?
6. Do you find you forget whether you’ve turned off a light or the stove or locked the door?
7. Do you fail to listen to people’s names when you are meeting them?
8. Do you say something and realize afterwards that it might be taken as insulting?
9. Do you fail to hear people speaking to you when you are doing something else?
10. Do you lose your temper and regret it?
11. Do you leave important letters unanswered for days?
12. Do you find you forget which way to turn on a road you know well but rarely use?
13. Do you fail to see what you want in a supermarket (although it’s there)?
14. Do you find yourself suddenly wondering whether you’ve used a word correctly?
15. Do you have trouble making up your mind?
16. Do you find you forget appointments?
17. Do you forget where you put something like a newspaper or a book?
18. Do you find you accidentally throw away the thing you want and keep what you meant to throw away—as in the example of throwing away the matchbook and putting the used match in your pocket?
19. Do you daydream when you ought to be listening to something?
20. Do you find you forget people’s names?
21. Do you start doing one thing at home and get distracted into doing something else (unintentionally)?
22. Do you find you can’t quite remember something although it’s ‘on the tip of your tongue’?
23. Do you find you forget what you came to the shops to buy?
24. Do you drop things?
25. Do you find you can’t think of anything to say?
Appendix H: Handedness Questionnaire

Please indicate which hand you habitually use for each of the following activities by choosing the appropriate number. "1"=Always Left, "2"=Usually Left, "3"=Left or Right Equally,"4"=Usually Right, "5"=Always Right

1. To write a letter legibly
2. To throw a ball to hit a target
3. To hold a racket in tennis, squash or badminton
4. To hold a match while striking it
5. To cut with scissors
6. To guide a thread through the eye of a needle (Or guide needle on to thread)
7. At the top of a broom while sweeping
8. At the top of a shovel when moving sand
9. To deal playing cards
10. To hammer a nail into wood
11. To hold a toothbrush while cleansing your teeth
12. To unscrew the lid of a jar
Appendix I: Early Adolescent Temperament Questionnaire

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E Adolescent Temperament Questionnaire - Revised
Short Form

Directions

On the following page you will find a series of statements that people might use to describe themselves. The statements refer to a wide number of activities and attitudes.

For each statement, please circle the answer that best describes how true each statement is for you. There are no best answers. People are very different in how they feel about these statements. Please circle the first answer that comes to you.

You will use the following scale to describe how true or false a statement is about you:

<table>
<thead>
<tr>
<th>Circle number:</th>
<th>If the statement is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Almost always untrue of you</td>
</tr>
<tr>
<td>2</td>
<td>Usually untrue of you</td>
</tr>
<tr>
<td>3</td>
<td>Sometimes true, sometimes untrue of you</td>
</tr>
<tr>
<td>4</td>
<td>Usually true of you</td>
</tr>
<tr>
<td>5</td>
<td>Almost always true of you</td>
</tr>
<tr>
<td>How true is each statement for you?</td>
<td>Almost always untrue</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>1) It is easy for me to really concentrate on homework problems.</td>
<td>1</td>
</tr>
<tr>
<td>2) I feel pretty happy most of the day.</td>
<td>1</td>
</tr>
<tr>
<td>3) I think it would be exciting to move to a new city.</td>
<td>1</td>
</tr>
<tr>
<td>4) I like to feel a warm breeze blowing on my face.</td>
<td>1</td>
</tr>
<tr>
<td>5) If I'm mad at somebody, I tend to say things that I know will hurt their feelings.</td>
<td>1</td>
</tr>
<tr>
<td>6) I notice even little changes taking place around me, like lights getting brighter in a room.</td>
<td>1</td>
</tr>
<tr>
<td>7) I have a hard time finishing things on time.</td>
<td>1</td>
</tr>
<tr>
<td>8) I feel shy with kids of the opposite sex.</td>
<td>1</td>
</tr>
<tr>
<td>9) When I am angry, I throw or break things.</td>
<td>1</td>
</tr>
<tr>
<td>10) It's hard for me not to open presents before I'm supposed to.</td>
<td>1</td>
</tr>
<tr>
<td>11) My friends seem to enjoy themselves more than I do.</td>
<td>1</td>
</tr>
<tr>
<td>12) I tend to notice little changes that other people do not notice.</td>
<td>1</td>
</tr>
<tr>
<td>13) If I get really mad at someone, I might hit them.</td>
<td>1</td>
</tr>
<tr>
<td>14) When someone tells me to stop doing something, it is easy for me to stop.</td>
<td>1</td>
</tr>
<tr>
<td>15) I feel shy about meeting new people.</td>
<td>1</td>
</tr>
<tr>
<td>16) I enjoy listening to the birds sing.</td>
<td>1</td>
</tr>
<tr>
<td>17) I want to be able to share my private thoughts with someone else.</td>
<td>1</td>
</tr>
<tr>
<td>18) I do something fun for a while before starting my homework, even when I'm not supposed to.</td>
<td>1</td>
</tr>
<tr>
<td>19) I wouldn't like living in a really big city, even if it was safe.</td>
<td>1</td>
</tr>
<tr>
<td>20) It often takes very little to make me feel like crying.</td>
<td>1</td>
</tr>
<tr>
<td>21) I am very aware of noises.</td>
<td>1</td>
</tr>
<tr>
<td>22) I tend to be rude to people I don't like.</td>
<td>1</td>
</tr>
<tr>
<td>23) I like to look at the pattern of clouds in the sky.</td>
<td>1</td>
</tr>
<tr>
<td>24) I can tell if another person is angry by their expression.</td>
<td>1</td>
</tr>
<tr>
<td>25) It bothers me when I try to make a phone call and the line is busy.</td>
<td>1</td>
</tr>
<tr>
<td>26) The more I try to stop myself from doing something I shouldn't, the more likely I am to do it.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>27</td>
<td>I enjoy exchanging hugs with people I like.</td>
</tr>
<tr>
<td>28</td>
<td>Skiing fast down a steep slope sounds scary to me.</td>
</tr>
<tr>
<td>29</td>
<td>I get sad more than other people realize.</td>
</tr>
<tr>
<td>30</td>
<td>If I have a hard assignment to do, I get started right away.</td>
</tr>
<tr>
<td>31</td>
<td>I will do most anything to help someone I care about.</td>
</tr>
<tr>
<td>32</td>
<td>I get frightened riding with a person who likes to speed.</td>
</tr>
<tr>
<td>33</td>
<td>I like to look at trees and walk amongst them.</td>
</tr>
<tr>
<td>34</td>
<td>I find it hard to shift gears when I go from one class to another at school.</td>
</tr>
<tr>
<td>35</td>
<td>I worry about my family when I'm not with them.</td>
</tr>
<tr>
<td>36</td>
<td>I get very upset if I want to do something and my parents won't let me.</td>
</tr>
<tr>
<td>37</td>
<td>I get sad when a lot of things are going wrong.</td>
</tr>
<tr>
<td>38</td>
<td>When trying to study, I have difficulty tuning out background noise and concentrating.</td>
</tr>
<tr>
<td>39</td>
<td>I finish my homework before the due date.</td>
</tr>
<tr>
<td>40</td>
<td>I worry about getting into trouble.</td>
</tr>
<tr>
<td>41</td>
<td>I am good at keeping track of several different things that are happening around me.</td>
</tr>
<tr>
<td>42</td>
<td>I would not be afraid to try a risky sport, like deep-sea diving.</td>
</tr>
<tr>
<td>43</td>
<td>It's easy for me to keep a secret.</td>
</tr>
<tr>
<td>44</td>
<td>It is important to me to have close relationships with other people.</td>
</tr>
<tr>
<td>45</td>
<td>I am shy.</td>
</tr>
<tr>
<td>46</td>
<td>I am nervous of some of the kids at school who push people into lockers and throw your books around.</td>
</tr>
<tr>
<td>47</td>
<td>I get irritated when I have to stop doing something that I am enjoying.</td>
</tr>
<tr>
<td>48</td>
<td>I wouldn't be afraid to try something like mountain climbing.</td>
</tr>
<tr>
<td>49</td>
<td>I put off working on projects until right before they're due.</td>
</tr>
<tr>
<td>50</td>
<td>When I'm really mad at a friend, I tend to explode at them.</td>
</tr>
<tr>
<td>51</td>
<td>I worry about my parent(s) dying or leaving me.</td>
</tr>
<tr>
<td>52</td>
<td>I enjoy going places where there are big crowds and lots of excitement.</td>
</tr>
<tr>
<td>53</td>
<td>I am not shy.</td>
</tr>
<tr>
<td>54</td>
<td>I am quite a warm and friendly person.</td>
</tr>
<tr>
<td>55</td>
<td>I feel sad even when I should be enjoying myself, like at Christmas or on a trip.</td>
</tr>
</tbody>
</table>
Appendix J: Schizotypal Personality Questionnaire

Please answer each item marking 0 for No and 1 for Yes. Answer all items even if unsure of your answer. When you have finished, check over each one to make sure you have answered them.

1. Do you sometimes feel that things you see on the TV or read in the newspaper have a special meaning for you?
2. I sometimes avoid going to places where there will be many people because I will get anxious.
3. Have you had experiences with the supernatural?
4. Have you often mistaken objects or shadows for people, or noises for voices?
5. Other people see me as slightly eccentric (odd).
6. I have little interest in getting to know other people.
7. People sometimes find it hard to understand what I am saying.
8. People sometimes find me aloof and distant.
9. I am sure I am being talked about behind my back.
10. I am aware that people notice me when I go out for a meal or to see a film.
11. I get very nervous when I have to make polite conversation.
12. Do you believe in telepathy (mind-reading)?
13. Have you ever had the sense that some person or force is around you, even though you cannot see anyone?
14. People sometimes comment on my unusual mannerisms and habits.
15. I prefer to keep to myself.
16. I sometimes jump quickly from one topic to another when speaking.
17. I am poor at expressing my true feelings by the way I talk and look.
18. Do you often feel that other people have got it in for you?
19. Do some people drop hints about you or say things with a double meaning?
20. Do you ever get nervous when someone is walking behind you?
21. Are you sometimes sure that other people can tell what you are thinking?
22. When you look at a person or yourself in a mirror, have you ever seen the face change right before your eyes?
23. Sometimes other people think that I am a little strange.
24. I am mostly quiet when with other people.
25. I sometimes forget what I am trying to say.
26. I rarely laugh and smile.
27. Do you sometimes get concerned that friends or co-workers are not really loyal or trustworthy?
28. Have you ever noticed a common event or object that seemed to be a special sign for you?
29. I get anxious when meeting people for the first time.
30. Do you believe in clairvoyancy (psychic forces, fortune telling)?
31. I often hear a voice speaking my thoughts aloud.
32. Some people think that I am a very bizarre person.
33. I find it hard to be emotionally close to other people.
34. I often ramble on too much when speaking.
35. My "non-verbal" communication (smiling and nodding during a Y N conversation) is poor.
36. I feel I have to be on my guard even with friends.
37. Do you sometimes see special meanings in advertisements, shop windows, or in the way things are arranged around you?
38. Do you often feel nervous when you are in a group of unfamiliar people?
39. Can other people feel your feelings when they are not there?
40. Have you ever seen things invisible to other people?
41. Do you feel that there is no-one you are really close to outside of your immediate family, or people you can confide in or talk to about personal problems?
42. Some people find me a bit vague and elusive during a conversation.
43. I am poor at returning social courtesies and gestures.
44. Do you often pick up hidden threats or put-downs from what people say or do?
45. When shopping, do you get the feeling that other people are taking notice of you?
46. I feel very uncomfortable in social situations involving unfamiliar people.
47. Have you had experiences with astrology, seeing the future, UFOs, ESP or a sixth sense?
48. Do everyday things seem unusually large or small?
49. Writing letters to friends is more trouble than it is worth.
50. I sometimes use words in unusual ways.
51. I tend to avoid eye contact when conversing with others.
52. Have you found that it is best not to let other people know too much about you?
53. When you see people talking to each other, do you often wonder if they are talking about you?
54. I would feel very anxious if I had to give a speech in front of a large group of people.
55. Have you ever felt that you are communicating with another person telepathically (by mind-reading)?
56. Does your sense of smell sometimes become unusually strong?
57. I tend to keep in the background on social occasions.
58. Do you tend to wander off the topic when having a conversation?
59. I often feel that others have it in for me.
60. Do you sometimes feel that other people are watching you?
61. Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?
62. I attach little importance to having close friends.
63. Do you sometimes feel that people are talking about you?
64. Are your thoughts sometimes so strong that you can almost hear them?
65. Do you often have to keep an eye out to stop people from taking advantage of you?
66. Do you feel that you are unable to get "close" to people?
67. I am an odd, unusual person.
68. I do not have an expressive and lively way of speaking.
69. I find it hard to communicate clearly what I want to say to people.
70. I have some eccentric (odd) habits.
71. I feel very uneasy talking to people I do not know well.
72. People occasionally comment that my conversation is confusing.
73. I tend to keep my feelings to myself.
74. People sometimes stare at me because of my odd appearance.