Synchronized Gamma Oscillations Underlying Mid-latency Auditory Evoked Potentials: Assessment of Effects of Psychopharmacologically Active Components of Tobacco

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(ABSTRACT)

The effects of smoking cigarettes on sensory gating, P50 and stimulus-bound gamma band (32-48 Hz) oscillations were examined in two paradigms: paired-tone and oddball. During a paired-tone paradigm, our previous work (Crawford, McClain-Furmanski, Castagnoli, & Castagnoli, Neuroscience Letters 317 (2002) 151-155) found heavy smokers exhibited chronic (rather than acute) effects in the frontal region: (1) larger P50 and GBO responses; (2) greater P50 and GBO sensory gating suppression, as well as earlier GBO sensory gating suppression. During an oddball paradigm, we (McClain-Furmanski, Crawford, Castagnoli & Castagnoli, in prep.) found an acute effect between 0 and 20 ms post-stimulus in the GBO, however we were unable to determine whether this effect was due to nicotine or the act of smoking.

In the present study, participants were 24 heavy cigarette (20+/day) right-handed, non-depressed smokers with no known medical or psychiatric problems, and no known familial history of psychiatric problems. In the morning, they were tested after abstaining overnight and after smoking a cigarette containing either 1.1 mg of nicotine, or a denicotinized cigarette (< 0.04 mg). In study 1 (oddball paradigm), although some effects were found related to nicotine and/or smoking, observed as condition by group interactions with the groups changing differently across conditions, they differed in temporal and spatial localization from those hypothesized. Thus, the present study was unable to differentiate between nicotine effects and effects due to the act of smoking. In study 2 (paired-pulse paradigm), in traditional evoked potential analysis, we observed significant chronic sensory gating, as measured by the ratio of N40-P50 amplitude in

response to the second tone (S2) as compared to the response to the first tone (S1). The effect was greatest at the hypothesized location (FCZ). In time series analysis of the underlying GBO, we replicated our earlier findings in that S2/S1 effects could be detected across 60 msec of the response. These results are discussed in relation to the neurochemistry and neural processes underlying sensory gating at GBO production, as well as in relation to the known and hypothesized psychopharmacological effects of smoking tobacco. Furthermore, these results are related to the theorized basis of addiction.

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"Deep and dark, yet within it there is an essence. This essence is real, and can be discovered. Therein lies belief." – Lao Tzu, Tao Te Ching

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Chapter 1: Introduction

Overview

Although the significant health risks associated with smoking tobacco are widely publicized, nearly 50 million Americans continue to smoke (Fiore, 1992). With more than 430,000 tobacco-related deaths per year, tobacco smoking is the leading preventable cause of death (Smith & Fiore, 1999). Many people who continue to smoke would prefer to quit, but find themselves strongly addicted. Tobacco addiction is among the hardest addictions to break, with a recidivism rate of 70% (USDHHS, 2000).

Some clinical populations use tobacco significantly more than non-clinical populations. Whereas 24% of the general population smokes, 70% of schizophrenics smoke (Adler et al., 1998), as do 42% of persons with attention deficit disorder (Lambert & Hartsough, 1998). Both of these disorders are frequently associated with deficiencies in ignoring or gating extraneous information. These persons, as well as many smokers (Edwards et al., 1985; Gilbert, 1994; Kassel, 1997), report that smoking improves their ability to concentrate and focus their attention. Nicotine may serve as an ameliorative for cognitive decline in Alzheimer's (for review, see Rezvani & Levin, 2001). Thus, tobacco smoking may serve a neurotherapeutic role in some groups or individuals.

Several epidemiological studies suggest that tobacco smokers contract Parkinson's disease at a rate of only 25% of that of non-smokers (e.g.,Morens et al., 1995). This may be due to the chronically inhibited monoamine oxidase (MAO) levels in smokers (Fowler et al., 1996; Fowler et al., 1998). Despite negative connotations due to harmful effects of smoking, tobacco remains a potentially important source of beneficial pharmaceuticals.

In order to determine how best to treat addiction to tobacco, understand what benefits some populations may obtain from its use, and determine what beneficial substances might be derived from the plant, it is necessary to determine the

psychopharmacological mechanisms impacted by tobacco smoking. Scalp-recorded electroencephalography (EEG), and extracted evoked potentials (EPs) are often used as markers in human psychopharmacological research, and serve as a means to probe and temporally track perceptual and cognitive processes that are affected by centrally acting agents. The present study examined the acute and chronic effects of smoking on auditory EPs and the underlying event related EEG synchronization, and related the obtained results to known and hypothesized neurochemical effects of nicotine and other components of tobacco smoke.

The following sections draw upon several diverse fields, which will be introduced separately, in order to provide a thorough background. These are then converged in order to support the experimental design.

Sensory Gating

Sensory gating is the action of brain mechanisms that modulate the flow of incoming sensory information. In general, the literature focuses on those mechanisms which block extraneous information. Over the years, two major sensory gating testing paradigms have been used in human and animal behavioral studies to quantify the amount of sensory gating: (1) the prepulse inhibition (PPI), which assesses the plasticity of the startle response; and (2) the reduction of the P50 mid-latency auditory EP to the second of a pair of closely spaced stimuli, which assesses a non-habituating suppression to the second evoked response. Although not functionally related (Ellenbroek et al., 1999), they are similarly sensitive to psychopharmacological manipulations.

PPI is a centrally mediated sensory gating mechanism (for review, see Swerdlow et al., 1998). It is observed as the inhibition of the startle reflex that occurs when a startling stimulus (e.g., very loud tone) is preceded by a weaker prestimulus (auditory, visual, or air puffs). PPI is considered to be an inhibitory process, and is known to be sensitive to the manipulation of dopamine (Zhang et al., 2000), which serves as an inhibitory neurotransmitter to the cortex's primary excitatory neurotransmitter,

acetylcholine. PPI is commonly tested by presenting pairs of stimuli approximately 500 msec apart, with 5 to 30 seconds between pairs to allow the startle response to recover.

The paired-stimuli PPI paradigm has been adapted to human evoked potential studies in order to examine changes in the exogenous, fronto-centrally located P50. The P50, also called the P1, occurs ~50 - 70 msec post-stimulus. When presented with pairs of identical clicks or tones in a design similar to PPI studies, the P50 response to the second stimulus (S2, or testing stimulus) is reduced as compared to the P50 response to the first stimulus (S1, or conditioning stimulus) (Freedman et al., 1987). The amount of reduction, typically taken as a ratio or percent measure of the P50 response to the first stimulus, is considered a measure of auditory sensory gating (e.g., Boutros & Belger, 1999, Freedman et al., 1998).

It has been generally assumed that the reduced P50 to the second stimulus signifies an inhibitory process that gates out sensory information. While this may be valid in some cases, evidence exists which indicates this is an incomplete picture. Specifically, Boutros and Belger (1999) have expanded the definition of sensory gating to refer to "the ability of the brain to modulate its sensitivity to incoming sensory stimuli" (p. 917). They point out that sensory gating may be subserved by two mechanisms: (1) gating out, which is the decreased responding to redundant or irrelevant stimuli, and (2) gating in, which is an increased responding to novel stimuli or a change in repetitive stimuli. Indeed, as discussed later, in our prior work (Crawford et al., 2002) we found that smokers had a greater P50 amplitude to S1 than did non-smokers, whereas there was no significant difference between groups in the P50 amplitude to S2.

The majority of studies which have investigated sensory gating deficits in schizophrenics, who often report accompanying difficulty in attentional processing and the blocking out of extraneous information or stimuli, use ratio or subtraction scores to determine degree of sensory gating and assume that differences are due to gating out mechanisms. Smoking normalizes the deficit in P50 reduction in these patients and decreases their negative symptoms (Adler et al., 1993). It is theorized that this is due to

dopaminergic activity (Lyon, 1999). After reviewing this literature, DeBruin et al. (2001) point out that these sensory gating deficits observed in schizophrenics may be due to decreased S1 (gating in) rather than decreased S2 (gating out) amplitudes.

The present study used the paired pulse P50 paradigm in order to assess sensory gating in non-clinical individuals who smoke. An example of P50 reduction in a paired tone paradigm is provided in Figure 1.

Event Related Synchronization

The brain's response to stimuli is manifested in changes in EEG. These changes can be analyzed using the classic, phase-locked EPs or by examining both phase-locked (evoked) and non-phase-locked (induced) oscillatory activity. The study of averaged EPs is based on the fact that in the averaging process, the "random" background activity averages to zero, leaving the time locked, synchronized response. The traditional analysis techniques were extended by several leading electrophysiologists (e.g., Basar, 1980; Basar & Bullock, 1992; Lopes da Silva & Pfurtscheller, 1999) to the study of event-related synchronization and desynchronization of EEG.

Neural activation may be divided into induced and evoked activation. Induced activation occurs when one functional cellular assembly transmits information and therefore activates another cellular assembly via subcortical channels. The resulting response is activation that is not synchronized, or in phase, with the transmitting cellular assembly, despite being stimulus bound and occurring within the same time frame. Thus, this is considered event-related desynchronization. Although this contributes to the EEG signal as recorded, such activation would not be apparent in traditionally constructed EPs (Lopes da Silva & Pfurtscheller, 1999).

Evoked activation occurs due to cortico-cortical activity, either between or within functional cellular assemblies, or due to incoming sensory information. It is stimulus bound and phase locked, and so does appear in EPs as event related synchronization

(Lopes da Silva & Pfurtscheller, 1999). However, the evoked synchronization may not necessarily appear as a single positive or negative component. This response may in fact appear as oscillatory activity, with several consecutive positive and negative deflections.

In as much as these oscillations represent ongoing neural processes (Singer, 1999), examination of such activity should take into consideration the entirety of the post stimulus EEG response. One should consider the amplitude of the oscillation as it waxes and wanes over the time course (i.e. modulation), rather than simply taking the amplitude of the individual components (e.g. Demiralp et al., 1996; Crawford et al., 2002). An example of event related synchronization resulting in oscillatory activity is provided in Figure 2.

One frequency range of EEG that has been studied in terms of its oscillatory behavior is the narrow gamma frequency response around 40 Hz. Gray and Singer (1989) showed that synchronization of these signals correlate to the activation of distal cellular assemblies that were previously shown to respond to the same stimulus. This widely distributed activity (Basar et al., 2001) was shown to be involved in both early and late perceptual processes (Singer & Gray, 1995), as well as arousal, perceptual integration, attentional selection and working memory (Engel & Singer, 2001).

Synchronized 40 Hz gamma activity is commonly hypothesized to be the "binding" response, which binds various sensory and cognitive signals into a unitary, gestalt perceptual experience (for review, see Bertrand & Tallon-Baudry, 2000). It is produced by inhibitory interneurons, primarily basket cells, which bind and synchronize functional cellular assemblies by inhibiting the firing of cells within the assembly which are out of synchrony (Llinás et al., 1991). The inhibitory activity of these cells on pyramidal neurons is via the release of gamma amino-butyric acid (GABA) (for review, see Buzsaki, 2001).

The concept of binding, and functional differences between induced and evoked activity, is supported by evidence from several commisurotomy studies by Sargent, as

reexamined by Liederman (1995). In these studies, commisurotomy patients were shown to have an implicit awareness in one hemisphere to stimuli presented to the other hemisphere. For example, in one study patients were presented with two letters to each visual field. They were able to determine whether the four letters formed a word, but were not able to name the two letters presented to the left visual field. In another study a face was first presented to the right visual field. Patients were able to answer yes/no questions about the face, such as age, sex, occupation and personality, but were not able to name the person. When the same face was presented to the left hemisphere, the person could immediately identify the person, but denied having seen the face before. In these studies it is clear that information is being transferred between hemispheres, but due to commisurotomy it is strictly via subcortical channels; there is no cortico-cortical transfer possible. This suggests that without the synchronization carried by the cortico-cortical connections the patients exhibit implicit awareness of the information transferred by induced activity, but not explicit awareness in the hemisphere opposite from presentation.

In the auditory system, 40 Hz activity has often been studied as the "transient 40 Hz response". This is seen as a stimulus-bound change in amplitude, increasing from pre-stimulus baseline levels to around 50 - 70 msec post-stimulus and decreasing back to baseline levels at about 100 to 120 msec post-stimulus (for review, see Tiitinen et al., 1997). This activity is most obvious in the fronto-central region and in the temporal cortex. It is enhanced by selective attention (Tiitinen et al., 1993) and gradually reduces in amplitude as vigilance decreases (May et al., 1994).

The transient 40 Hz response was shown to be sensitive to various psychotropic substances that are capable of impacting attentional and cognitive functioning. The drug-related changes in behavior known to be associated with these substances correlate with observed changes in the transient 40 Hz response. Sedating drugs such as ethanol (Jääskeläinen et al., 2000), haloperidol (Ahveninen, 2000), and the benzodiazapine temazepam (Jääskeläinen et al., 1999) suppressed this response. On the other hand, the stimulant scopolamine augmented the 40-Hz response (Ahveninen et al., 1999, 2002).

These studies assessed data obtained from the well known oddball paradigm, in which a small proportion (typically 10% to 20%) of auditory tones differ from the majority of tones presented by a chosen characteristic such as volume, pitch, duration, location, etc. This paradigm is also used in studies of mismatch negativity (MMN), an EP component that is elicited by the unusual (oddball) stimulus and appears as a negativity lasting from approximately 100 msec to 250 msec post-stimulus (Näätänen, 1992). In their review, Tiitinen et al. (1997) concluded that the transient 40 Hz response was related to stimulus detection, but not sensitive to stimulus characteristics, as is the MMN.

When an auditory EP is analyzed in the traditional manner, the mid-latency components appear as several sequential positive and negative peaks in the first 100 msec (Näätänen, 1992). When an auditory EP (AEP) is high pass filtered at 10 Hz, to remove the effect of the larger, slow deflections of the N100 and P200 and thereby better view the smaller mid-latency responses (Freedman et al., 1998), additional negative (~70 msec) and positive (~90 msec) peaks may appear. Some researchers (Clementz et al., 1997; Demiralp, Basar-Eroglu & Basar, 1996; Crawford et al., 2002) have noted that the mid-latency auditory evoked potentials N0, P0, Na, Pa, Nb and P1 or P50 (at about 9, 15, 19, 32, 40 and 50 msec post stimulus) may be related to the mechanism contributing to the transient 40 Hz response. If this is the case, then these components should not be considered as being independent. Rather, they should be examined as a collection of sequential positive and negative going peaks, the modulation of which represents more or less synchronization of the generator(s) of the 40 Hz signal across the entire time span of the response.

It should be noted that when the AEP is bandpass filtered to remove the influence of the N100 onset, the portion of the signal being filtered out could begin as early as 30 msec post stimulus. Furthermore, the effect is non-linear, in that this deflection begins as a positivity lasting until approximately 70 to 80 msec, at which point it becomes a negativity representing the N100 onset. When the 10 Hz high pass filter is applied, the transformed waveform is changed in such a way that the signal from the original baseline differs for different points along the time series. For this reason, taking P50 amplitude as

a peak-to-peak measure, as opposed to an amplitude difference from the pre-stimulus baseline, may provide a more accurate measurement of the P50 component. This study examined P50 suppression as analyzed in both the traditional manner, as a bandpass filtered EP, and as synchronization of 40 Hz activity, in order to provide a comparison of the results that can be obtained from both methods.

Quantifying Oscillations: MAVA

Quantifying oscillatory activity challenges our traditional concepts of evoked response analysis. The activity of interest is the waxing and waning of the amplitude of the oscillation, representing greater or lesser synchronization, which occurs contiguously across time. Thus, the usual peak amplitude and latency measures provide far fewer data points and do not reflect the extended temporal nature of the oscillation.

Several approaches have been used to characterize oscillatory activity. Spectral analysis via fast Fourier transform (FFT) has been used by many (e.g., Pantev et al., 1991). This provides a single measure of the mean amplitude (or power) across a selected range of frequencies. However, this transform loses all time domain information. Furthermore, the selection of the time period over which to transform is critical, because the inclusion of too many signals that do not represent the evoked response will reduce the resulting data values. Also, adequate spectral resolution of the FFT requires sufficient data points, typically 256 (for 2 Hz resolution) or 512 (for 1 Hz resolution). Analysis of a 100 msec sample with good resolution requires an extremely fast sampling rate (well over 1000 Hz), which until recently has been beyond the capability of most researchers' equipment. While spectral analysis can be used to perform useful comparisons, it is insufficient for characterizing the oscillation.

Näätänen and colleagues have assessed a mean gamma frequency amplitude over a restricted range of the transient 40 Hz response, such as from 30 to 130 msec (Ahveninen et al., 2000; Näätänen, 1992). However, this provides only a single datum.

Again, while useful for comparisons in overall response, it fails to capture the temporal dynamics of the response.

In order to accomplish analyses with greater temporal resolution, mean absolute value amplitude (MAVA) analysis can be applied to the signal (Crawford et al., 2002). In MAVA, a signal of interest is band pass filtered to the desired range, and rectified to produce all positive values. Due to rectification there is an artificial doubling of the apparent frequency. The response is then refiltered with a low pass filter set at the same low pass cut off as the original band pass filter, to remove this artifact of analysis. What remains is a time series representing the averaged changes in amplitude modulation across the period of the epochs that comprise the averaged evoked response. This produces a measure of the changes in synchronization in the same units of measure as the traditionally analyzed averaged evoked potentials. Although of a different amplitude, differences noted in each measurement technique can be accurately compared and correlated, as they are proportional measures. While it is possible to perform statistical analyses of the signals thus transformed down to the resolution of the sampling rate, most often the signal is examined within arbitrarily chosen time windows, with the amplitude averaged within the window. A comparison of an oscillation with a MAVA transform applied to it is provided in Figure 3.

Strictly speaking, the second filtering process is not necessary to the quantification process; similar numerical results could be obtained by averaging within time windows on the rectified data. This is, in fact, what Näätänen and colleagues do, within a single time window (e.g. Ahveninen et al., 2000). However, by filtering out the peaks, and thereby leaving only the modulation, a cleaner visual presentation of the modulation is obtained, and graphic representation, particularly of multiple tracings, is much clearer. In as much as the processes produce similar numerical results, and the additional filtering in MAVA does not produce artifact within the signal of interest, this approach is preferable.

The MAVA technique, and indeed all of digital filtering, is susceptible to two forms of induced artifact, phase shift and edge artifact. Phase shift, which appears as a consistent shift of the post-filtering signal along the time axis, is easily remedied by the use of two-pole filtering. When the filter is applied, it is applied twice, starting from either end of the sample. This produces phase shift artifact in both, of the same amount but in opposite directions. The results are averaged together across the time domain, canceling out the phase shift.

Edge artifact is not so much remedied as it is ignored. It occurs within the last half wavelength of the lowest frequency component of the post-filter signal, and when present, appears as an excessive amplitude increase in the signal. By selecting a sample time window that leaves room for this artifact without degrading any portion of the signal undergoing analysis, this can be ignored.

Neurochemistry and Electrophysiology of Smoking

The primary psychoactive ingredient in tobacco is nicotine. Tobacco acts as a cholinergic agonist directly through the action of nicotine on nicotinic acetylcholine receptors. This is manifested in human EEG as global changes in cortical activity (Knott et al., 1998). Smoking tobacco results in a rapid increase in nicotine in the blood. Lunell et al. (2000) showed that after smoking, nicotine levels peaked in the brachial artery at 4.0 +/- 0.6 minutes, and at the jugular vein at 6.4 +/- 0.4 minutes, giving an estimate of peak nicotine levels in cortical capillaries, and thus the blood-brain barrier, at 5.2 +/- 0.5 minutes. Furthermore, because nicotinic receptors desensitize within seconds following exposure (Lester and Dani, 1995; Mansvelder & McGehee, 2000), the global rate of desensitization would very closely follow the increase in concentration. Thus, any direct nicotine induced cholinergic activation is likely to be short lived.

Smoking tobacco also produces a reciprocal effect on the dopaminergic system via nicotinic acetylcholine receptors located on dopaminergic neurons (Jones et al., 1999). Dopaminergic activity that is related to frontal psychomotor activation is

considered to be the mechanism underlying addictive behavior (Wise & Bozarth, 1987; for review see Jentsch & Taylor, 1999). Smoking is known to increase P50 suppression in healthy subjects, and to normalize deficient P50 suppression in schizophrenics (Adler et al., 1998). Again, because this effect relies on direct action on nicotinic receptors, it too should be relatively short lived. In as much as smokers exhibit chronic differences in EEG as compared to non-smokers, even after overnight abstention (Crawford et al., 2002), nicotine alone cannot account for the differences. Other neurochemical processes must be considered.

Of particular interest is monoamine oxidase (MAO), an enzyme that catalyzes the oxidative deamination of brain amines. This enzyme system occurs in two forms (A and B) (for review, see Berlin & Anthenelli, 2001). MAO-A, which comprises 70% of neuronal MAO, and is found in the liver as well as neural tissue, preferentially catalyzes the deamination of norepinephrine (NE), epinephrine (E) and serotonin (5-HT). MAO-B, which is found in glial cells and in blood platelets, preferentially catalyzes the deamination of benzylamine and phenylethylamine (PEA). MAO-B activity in blood platelets has been shown to correlate with MAO-B activity in the brain. Dopamine (DA) is a substrate for both the A and B forms of this enzyme.

Smoking tobacco leads to the chronic inhibition of MAO-A and MAO-B (for review, see Berlin & Anthenelli, 2001). The first study to demonstrate that platelet MAO activity was reduced in smokers was done by Oreland et al. (1981). In a review of published studies, smokers show a 20% to 30% reduction in MAO-A activity, and a 30% to 40% reduction in MAO-B activity (Berlin & Anthenelli, 2001). Similar blood platelet findings have recently been observed by Castagnoli and colleagues (unpublished data).

It has been shown that one or more constituents of smoking tobacco chronically inhibit the activity of both MAO-A and MAO-B in the brain (Fowler et al., 1996; Fowler et al., 1998). One such tobacco component has been identified as 2,3,6-trimethyl-1,4-naphthoquinone (Khalil et al., 2000). The inhibition of MAO activity, and the resulting reduction in the metabolism of brain amine neurotransmitters, could result in increased

levels of the amine neurotransmitters. Indeed, smokers show increased levels of NE, consistent with the physiological arousal effects noted, and increased levels of 5-HT, which influences mood and may be a factor that explains in part the correlation between smoking and depression (for review, see Benowitz, 1999). Furthermore, and most pertinent to the present work, smokers show higher levels of dopamine (Oreland et al., 1999). This could be manifested in EEG as changes in the systems driven by dopaminergic activity, such as enhancement of P50 suppression. Indeed, such evidence exists in studies of sensory gating (Lyon, 1999).

MAO activity changes relatively slowly. Fowler et al. (2000) found that overnight abstention had no effect on brain MAO-B activity in smokers. Thus, we would expect the impact on EEG to appear as a chronic dopaminergic effect. If so, it should be observable as chronic differences between smokers and non-smokers, even after nicotine depletion due to overnight abstention. This is the effect noted in our prior work (Crawford et al., 2002). However, given a long enough time span, MAO activity does change. Oreland et al. (1981) showed that while MAO activity was lower in smokers than non-smokers and ex-smokers, there was no difference between non-smokers and ex-smokers. This suggests a possible reversal of MAO inhibition after smoking cessation, although the amount of time involved has yet to be determined.

Furthermore, smoking tobacco is known to have a GABAergic effect. Nicotine was shown to pre-synaptically enhance electrically evoked GABAergic transmission at doses similar to those found in the blood levels of smokers, but that this effect was reversed at doses only twice that (Zhu & Chiappinelli, 1999). This is supported by evidence showing that nicotine is anxiolytic at doses that enhance GABAergic transmission, while at doses that diminish transmission, nicotine is anxiogenic (File et al., 1998).

This enhanced GABAergic transmission could be manifested as changes in the 40 Hz gamma band synchronization due to activation of the GABAergic inhibitory interneurons that mediate this response (Llinás et al., 1991). Because this effect is based

on pre-synaptic nicotine activation, it too should be sensitive to nicotine blood levels and be relatively short lived. Evidence showed that nicotine induced GABA release is sensitive to nicotine levels, but diminishes rapidly, lasting no longer than 2.5 minutes (Kayadjanian, 1994). Our prior work detected an increased transient 40 Hz response, within the first 20 msec post stimulus, in smokers after smoking, when tested within five minutes after smoking (McClain-Furmanski et al., in preparation). However, a second task, which was presented 5 to 10 minutes after smoking, did not show this effect (Crawford et al., 2002).

Nicotine also impacts the glutamate system by activating nicotinic receptors on dopaminergic neurons in the ventral tegmentum, which then are sensitized to glutamate input. When the released glutamate also activates N-methyl-D-aspartame (NMDA) receptors, long term potentiation can occur (Mansvelder & McGehee, 2000). This occurs during gamma frequency synchronization of slow EEG theta wave generators. Although this does not cause specific EEG changes itself, it does sensitize dopaminergic neurons and causes an increase in the time span of excitation, over and above that which would be expected by direct nicotinic receptor activation (Jensen & Lisman, 1996). Thus, these chronic dopaminergic effects may be reflected in enhanced P50 and transient 40 Hz responses.

The observed effects of NMDA potentiation on EEG theta activity (primarily of the hippocampus), taken with dopaminergic effects on the reward system, may have implications for the development and maintenance of addiction. They could potentially cause a parallel increase in reward system activation and long term potentiation, and thereby enhance the association between behavior (drug use) and reward (drug effect).

Paradoxical Reactions

Studies of sensory gating demonstrate that dopamine agonists impair P50 suppression (for review, see Swerdlow et al., 1994). The drugs employed typically have one or more actions, as dopamine releasing agents, reuptake inhibitors or receptor

agonists of one or more dopamine receptors. Dopamine agonist administration typically involves an acute reaction following administration to a naïve participant. This forces dopamine levels to increase far above normal.

Stimulants, such as amphetamine (a dopamine release agonist and re-uptake inhibitor), increase locomotor activity and exploratory activity (Wise & Bozarth, 1987). Such activity has an inverse relationship with the directed sensory activity of orienting. Disruption of sensory gating in naïve participants due to acute stimulant administration is thus supported behaviorally.

However, the effect of an amphetamine challenge in a naïve subject is contradicted by the effect of psychostimulants on individuals with attention deficit disorder. These individuals display a chronic deficit in the ability to ignore extraneous stimuli, with some also exhibiting hyperactivity. Dopaminergic psychostimulants, such as amphetamines and methylphenidate, can normalize these symptoms. In addition, smoking is known to enhance P50 suppression (Adler et al., 1993) and this effect is attributed to a dopaminergic action (Lyon, 1999).

This apparent contradiction is resolved by considering the acute and chronic effects of stimulated release and inhibited re-uptake. In an acute situation, excess dopamine infuses the synapse. This impacts the post-synaptic receptors, but also the pre-synaptic autoreceptors. The latter serves to inhibit further release, and thus produces a net paradoxical antagonist action. With chronic use, receptor down-regulation would occur due to chronic high levels of dopamine. Release would still be stimulated, but pre-synaptic inhibition would decrease, as would the paradoxical antagonist action. The system would normalize to a higher net level of dopamine.

In contrast, the dopaminergic action of MAO inhibition increases bioavailability (Cooper et al., 1996). Release is not acutely stimulated above normal levels and thus no paradoxical impact is seen. Also, with chronic, repeated administration, dopamine levels change slowly, allowing receptor re-regulation to occur as dopamine levels rise. The net

result would be chronic higher dopamine levels. Support for bioavailability increasing dopaminergic activity and normalizing dysfunction without disrupting sensory gating comes from the use of L-DOPA in Parkinson's disease (Cooper et al., 1996). L-DOPA is the primary precursor for dopamine. Administration stimulates more dopamine production and thus increases dopamine bioavailability, but does not stimulate release. Dopamine levels rise slowly, allowing the system to re-regulate. The net behavioral result is an improvement in deficient motor and cognitive control.

It is proposed herein that the loss of P50 suppression, upon the administration of dopaminergics, would be due to the deleterious paradoxical effects of acute administration above normal levels. Furthermore, it is proposed that the dopaminergic system re-regulation due to increased bioavailability results in greater inhibitory processing underlying sensory gating and P50 suppression. Given this, it was hypothesized that the inhibitory effects on P50 suppression and underlying gamma frequency oscillations in smokers would be observed as a chronic effect.

Neurophysiology of Addiction

A behavioral theory of addiction, based on what was called the "facilitation of approach and avoidance behaviors", was first proposed by Schneirla in 1959. Although not stated in terms of Skinnerian reinforcement, it is clear that the events he called stimulus events are what Skinner called positive reinforcers.

After reviewing animal studies that showed that electrical stimulation of the medial forebrain bundle instigated approach behavior, Glickman and Schiff (1967) proposed a biological basis for Schnierla's theory. The behaviors initiated by stimulation were eating, drinking, mating behavior, predatory attack, nest building, and sequential generalized forward locomotion towards the most salient objects in the environment. Although some are complex behaviors and others are simpler behaviors, the component common to all is approach behavior.

In a review of the drug literature, Wise and Bozarth (1987) extended this theory to addiction. They concluded that all drugs with addiction potential elicit psychomotor stimulation via the same tract as reward mechanisms, and that psychomotor stimulation is homologous with positive reinforcement. Although not addressed by Wise and Bozarth, the lateralization of approach and avoidance systems is of potential importance when considering drug addiction including tobacco smoking.

Rather consistent evidence indicates that positive evaluations, leading to positive motivational/affective states and approach behavior, are predominantly left frontal, whereas negative evaluations, leading to negative affect and avoidance behavior are right frontal in origin. Neuropsychological assessment of stroke patients (Robinson & Downhill, 1995), hemispheric deactivation via the Wada technique (Ahern et al., 2000) and EEG response to affectively valent stimuli (e.g., Davidson, 1995) support such a hemispheric specialization hypothesis.

In a recent review, Cacioppo and Gardner (1999) concluded that "Physical limitations may constrain behavioral expressions and incline behavioral predispositions toward a bipolar organization, but these limiting conditions appear to lose their power at the level of underlying mechanisms, where a bivalent approach may provide a more comprehensive account of the affect system" (p. 191). Two different mechanisms may underlie the evaluation of stimuli and subsequent production of responses: (1) the parallel, valency differentiated bilateral frontal systems, and (2) the stimulus evaluation and response formation right hemisphere system. The literature suggests that those studies that observe consistent right hemisphere predominance in EEG alpha response to affectively valent stimuli incorporate tasks that overtly or covertly elicit a behavioral response. On the other hand, those studies that show left approach/right avoidance hemispheric specialization of the frontal brain region examine either stimulus evaluation (per Davidson) or a prestimulus biasing of stimulus evaluation (and therefore response formation) due to disruption of the neural processing at the evaluation stage.

Various neuroimaging studies provide evidence for differences in the brains of smokers as compared to non-smokers, as well as evidence for nicotinic activation of the reward system. In a positron emission tomography (PET) of dopamine uptake, Salokangas et al. (2000) found that smokers had significantly greater dopamine activity in the basal ganglia than non-smokers, specifically the putamen (17.3% greater) and caudate (30.4% greater). Using PET, and the D1 receptor ligand [11C] SCH 23390, Dagher et al. (2001) found that smokers had reduced dopamine D1 receptor binding in the ventral striatum. While this result should be expected from down-regulation of receptors due to chronic higher dopamine levels, this could also be suggestive of a genetically determined difference that predisposes some individuals to become smokers.

Using PET as a means to assess regional cerebral blood flow, Martin-Soelch et al. (2001) evaluated smokers and non-smokers during a pre-learned pattern recognition task under conditions of monetary reward and no monetary reward. They found that while monetary reward activated reward-related regions such as the striatum in non-smokers, smokers showed no such increase. Although acknowledging this could be due to a predisposing factor, they concluded that the evidence was stronger for the difference being due to the effect of smoking per se.

In smokers who had abstained overnight, a 1 to 2 mg dose of nasal-spray nicotine caused an increase in glucose metabolism in the left inferior frontal gyrus, left posterior cingulate, and right thalamus (Domino et al., 2000). Similarly, after nicotine nasal spray, Zubieta et al. (2001) found increased rCBF in the right thalamus, and reduced rCBF in the left anterior temporal cortex. The thalamus is known to have a high concentration of nicotinic receptors, and the left frontal and anterior temporal regions are associated with limbic and paralimbic processing. An earlier study by Isaka et al. (1993) showed a reduction in right hemisphere rCBF following cigarette smoking. This could be interpreted as a greater relative left to right hemisphere involvement among smokers than non-smokers.

Given the above findings, one might expect a greater left frontal activation after smoking; such an enhancement would represent a prestimulus positive/approach biasing of neutral stimulus evaluation due to psychomotor stimulant induced activation. This pattern of activation implies the involvement of the dopaminergic reward mechanism, as should be expected from administration of a drug that affords self-reported satisfaction, and has addictive liability. In the present study, it was expected that this response would be manifested in the synchronization of the 40 Hz gamma activity, as it has been shown (as previously reviewed) to represent GABAergic recruitment of functional cellular assemblies within the reward system into synchronized action.

Smoking and EEG Research

The impact of nicotine and/or smoking tobacco on EEG brain activity has been documented for over 60 years. In 1939 (Bertrand, Delay & Guillain), a French handbook entitled "L'electroencephallogramme normal et pathologique" (The Normal and Pathological Electroencephalogram) listed nicotine among those drugs that induced significant changes in EEG. A paradoxical effect that is now well known in tobacco research may have been first reported by Murphree et al. (1967): although smokers claim that smoking is relaxing, their EEG mimics that of greater arousal. Interestingly, this study also noted that EEG changes happened very soon after smoke inhalation, even before blood borne pharmacological effects could be observed.

Numerous studies examining the impact of nicotine or smoking on EEG as measured by spectral analysis, or quantitative EEG, have typically shown a similar overall pattern to that observed by Murphree et al. (1967). In general, lower EEG frequencies are reduced while higher frequencies are enhanced (e.g., Pritchard, 1991; Norton et al., 1992). This pattern of activation is commonly noted as being similar to that of heightened arousal. Furthermore, other traditional physiological measures of arousal, such as heart rate and blood pressure, corroborate this arousal effect (e.g., Kadoya et al., 1994). Interestingly, when patients with Alzheimer's disease were given 2 mg nicotine

gum, their EEG activation profile appeared to be similar to that which is seen immediately after smoking in normal individuals (Knott et al., 2000).

In an attempt to localize and better characterize EEG changes after smoking, Domino et al. (1992) assessed low alpha (8-10 Hz) that is associated with arousal and high alpha (10-12 Hz) that is associated with cognitive processing. They found smoking reduced low alpha and augmented high alpha. Furthermore, peak alpha frequency increased in a dose dependent manner. An unexpected, but highly relevant, result highlighted the importance of evaluating individual differences in EEG activation before and after tobacco smoking. Some participants showed a global EEG activation pattern after smoking, while others exhibited a pattern that was primarily localized to the occipital region.

These findings were replicated and clarified further by Shikata et al. (1995). While low alpha reduced and high alpha increased following smoking, they observed that low and high beta were also augmented. Houlihan et al. (2001) examined activation in these frequency bands in a study comparing denicotinized cigarettes with cigarettes of normal nicotine yield. They found that high alpha and both beta bands increased after smoking normal yield cigarettes, but that high beta also increased after smoking denicotinized cigarettes. This suggests that either inhaling per se or some additional, unknown component in tobacco other than nicotine may have an impact upon EEG activation after smoking. Robinson et al. (1992) showed that the normally observed EEG and heart rate changes associated with smoking did not occur when participants were given denicotinized cigarettes. Furthermore, Pickworth et al. (1986) found increases in alpha and beta frequencies after chewing nicotine-containing gum. This effect is partially blocked by pre-administration of the nicotine antagonist mecamylamine (Pickworth et al., 1988).

Of particular note, when using auditory cues that had previously been paired with a reward of smoking, Mucha et al. (1998) found an increase in high beta as a conditioned

response. However, they did not observe changes in other physiological measures such as heart rate, skin conductance and EMG after the cue.

Studies of EEG activation during cognitive performance may further assist our understanding of the impact of smoking on EEG activity. Increased low alpha is often associated with poorer cognitive performance (Bosel, 1992; Klimesch et al., 1990). During tracking and decision making tasks, those individuals with self-reported poorer sustained attentional capabilities showed significantly higher low alpha response than did those individuals who reported high sustained attention capabilities (Crawford et al., 1995; Crawford & Vasilescu, 1995). Changes in low alpha were shown to correspond to changes in alertness (Gale & Edwards, 1983). Furthermore, increases in peak alpha frequency (i.e. decrease in low alpha and/or increase in high alpha) are related to better memory performance (Klimesch et al., 1993).

Vasquez-Marrufo et al. (2001) found that an increase in beta activity and a decrease in alpha activity occurred during a visual task. These results were more pronounced when the stimuli were attended to as opposed to being ignored. Furthermore, increases in upper alpha and certain beta frequency bands were associated with attentional effort and/or attentional abilities (e.g., Crawford et al., 1996). The field of neurofeedback (EEG biofeedback) centers on the training of individuals with attention deficit disorder to produce an increase in beta amplitude (often in a ratio comparison to theta amplitude) in an effort to retrain the brain and overcome symptoms (Lubar, 1997; Egner & Gruzelier, 2001).

Taken together, these findings suggest that the EEG changes seen in smoking are similar to those changes seen accompanying increased alertness, in effort and in better memory performance. Smokers commonly report feeling enhanced alertness and better focused attention (Foulds & Ghodse, 1995). In agreement with these reports and observed changes in EEG activity, smoking tobacco has been shown to facilitate early sensory gating and subsequent information processing (for review, see Heishman et al., 1994).

Coming from a dynamic systems approach, EEG has also been analyzed in terms of its nonlinear dynamics. Houlihan et al. (1996) found that nonlinearity, which is taken to be a measurement of the strength of relationship between all changes across a time series, no matter how far separated in time, was not affected by smoking. However, dimensional complexity (DCx), considered to be an estimate of the number of processes underlying a time series (i.e. the number of variables needed to describe it), showed a highly unusual effect. Smoking led to a "regression to the mean" effect. When DCx was low while abstaining, smoking increased it. When DCx was high while abstaining, smoking decreased it. When DCx was at an intermediate level while abstaining, smoking caused no changes. When these measures were re-examined after having the participants smoke a second cigarette, there were no additional changes. This suggests a normalization of state in abstaining smokers after one cigarette, possibly indicating withdrawal relief, and an acute tolerance effect with no differences after the second. In a second group of participants who received denicotinized cigarettes, no changes were observed.

Another common approach in the examination of the effects of smoking on brain activity is the analysis of evoked potentials to visual, somatosensory or auditory stimuli. Long-term smokers demonstrated a decreased visual P300, an indicator of the updating of working memory or context relevance, in comparison to ex-smokers and non-smokers (Anokhin et al., 2000). Houlihan et al. (1996) found increased amplitude and decreased latency in visual P300s after smoking, suggesting an enhanced detection of novelty or deviance. Once again, these changes were not seen in participants given denicotinized cigarettes.

Inconsistent findings across similar EP studies are also observed. For instance, Golding (1988) showed that while smoking produced the previously discussed increase in peak alpha frequency, sham smoking did not. By contrast, no changes in visual EPs were observed. Similarly, Lindgren et al. (1998) found an increase in high alpha and decrease in low alpha with the administration of oral snuff. When visual and auditory P300 EPs in a bimodal oddball task were assessed, they found no changes between conditions of

abstaining and chewing. They did note an increase in the auditory N2 amplitude to the deviant stimuli, a result which could indicate improved tone discrimination after nicotine.

During a short term memory task after smoking, Houlihan et al. (2001) found decreased latencies and increased amplitudes in visual cognitive N200 EPs to negative probes (items not previously seen), and increased P300 amplitudes to all probes, both of which were taken to be indicative of faster stimulus evaluation. Additionally, there was a decreased reaction time after smoking. They concluded that this was due to nicotine affecting response related processes, in that the difference in reaction time was far greater than the change in EP latency, and in light of the fact that short term memory scanning speed was not affected by smoking. Once again, they concluded this was a nicotine effect, as the changes noted were not found in a group that received denicotinized cigarettes.

Little work has addressed the impact of smoking on somatosensory EPs. Nicotine has long been known to induce analgesia, particularly in animals (e.g., Mattila et al., 1968), whereas nicotine withdrawal may induce hyperalgesia (Schmidt et al., 2001). In a group of habitual female smokers, Knott (1990) observed smoking increased EP amplitudes but did not impact ratings of pain levels. Knott and De Lugt (1991) examined N1-P2 amplitudes to somatosensory EPs created by painful electrical stimuli, and found no direct smoking related changes. Leon et al. (1998) found that the N18 wave disappeared soon after smoking and reappeared 10 minutes later. In an EP study of painful olfatory stimuli, at low and medium doses of nicotine the greatest amplitudes were seen in the parietal region, whereas at highest doses amplitudes were seen at CZ (Hummel et al., 1992).

Turning now to studies of the auditory system, an impact on early, middle and late EPs have been observed, albeit inconsistently, in numerous studies. In studying brain stem auditory EPs that occur within the first 10 msec post stimulus, Knott (1987) found that components I and III were not affected by smoking, but that component V appeared to increase after smoking. Further analysis showed that this was due to a smoking

induced resistance of component V to habituation to repeated stimuli, rather than an enhanced response. Since attention has been shown to modulate the response of component V (Lukas, 1980), one could conclude that these data suggest a smoking related enhancement of attention or vigilance.

In an examination of the entire auditory processing system, Harkrider and colleagues in a series of three related papers assessed the effects of transdermal nicotine on non-smokers. While otoacoustic emissions were not affected by nicotine administration, Harkrider et al. (2001) found that the wave I of the brain stem response was reduced in amplitude and had a longer latency. Additionally, the Na-Pa (N19-P30) amplitude and Nb latency were increased, as was the peak-to-peak amplitude of the 40 Hz response (Harkrider & Champlin, 2001a). Finally, the P1-N1 (P50-N100) amplitude increased, the N2 latency decreased, and the dominant (peak) alpha frequency increased (Harkrider & Champlin, 2001b). Taken together, their conclusion was that nicotine administration increased cortical activation due to increased arousal, and improved stimulus detection and discrimination.

The fronto-centrally located mid-latency component of the auditory EP is often tied to an evaluation of sensory gating by examination of the P50, as discussed previously. Dopamine-related abnormalities in sensory gating are normalized with a nicotine patch (Griffith et al., 1998) and smoking cigarettes (Adler et al., 1993) in schizophrenics (for review, see Adler et al., 1998). Furthermore, using nicotine-containing gum, Adler et al. (1993) found normalization among relatives of schizophrenics. As discussed below in greater detail, we (Crawford et al., 2002) found that healthy, non-psychiatric smokers exhibited chronic effects of greater cortical activation (larger P50 to S1 but not S2) and greater sensory gating when abstaining or after smoking one's own cigarette.

The auditory MMN has only recently been examined with respect to nicotine. Engeland et al. (2002), in a population of Alzheimer's patients, found a decrease in MMN latency after administration of nicotine chewing gum. Similarly, we (McClain-

Furmanski et al., in preparation) found a decrease in MMN latency in smokers as compared to non-smokers. MMN latency is a marker of stimulus deviance, with latency decreasing with increasing deviance. Taken together, these results suggest that nicotine may increase the ability to complete a sensory discrimination of a deviant stimulus.

Later auditory EP components, specifically the P300, appear not to be affected by tobacco. Knott et al. (1999) found that the P300 was not affected by the number of years that a person smoked. Houlihan et al. (1996) and Lindgren et al. (1999) found no change between the P300 between abstaining overnight and smoking a cigarette. Similarly, in our own work, we did not observe any impact on the auditory P300 in an oddball paradigm. This may be due to the choice of the paradigm in that the stimuli presented were redundant and not needful of context updating.

Preliminary Tobacco Smoking and EEG Studies from Our Laboratory

Our research program has emphasized the effects of tobacco smoking on sensory gating and transient 40-Hz response in two paradigms: the oddball and paired-pulse paradigms. In our first studies, we had heavy smokers abstain overnight. They were first tested in an abstaining state followed by a state in which they had just smoked their own cigarette. Non-smokers were tested in a similar fashion but without the administration of tobacco. The present study extended this research to assess the impact of nicotine vs. denicotinized cigarettes on sensory gating and transient 40-Hz responses in heavy smokers. The present work focused on the direct pharamcological effects of smoking on the dopaminergic system. Although the present work did examine a nicotinic effect, it also assessed chronic effects thought to be dopaminergic in order to demonstrate that these effects changed differentially across conditions.

In the oddball task, there were 80% standards and 15% deviant auditory stimuli, with 5% additional visual deviants to help center attention away from the sounds. This task elicits a stream of constant, regulated transient 40 Hz responses that are not sensitive to stimulus characteristics (Tiitinen et al., 1997). In this way we were able to obtain the

transient 40 Hz data while simultaneously obtain data related to MMN research. Because the transient 40 Hz response is sensitive to selective and sustained attention (Tiitinen et al., 1997), participants were instructed to place all their attention on the checkerboard visual stimuli and push a button whenever it reversed. This permitted us to control the effect of attention and keep it constant, as opposed to the less controlled situation where participants are given no attentional task and their attention may wander.

In the paired-pulse paradigm, there were pairs of tones, 512 ms apart from one another, with an interstimulus interval of 5 seconds. This paradigm was used, as it is the classic in the P50 sensory gating schizophrenia literature. As our prior research progressed, we became aware of the importance of the contribution of the transient 40-Hz response to the components contributing to the P50 response.

In our first published study (Crawford et al., 2002), we found that smokers, regardless of abstaining or having just smoked, showed consistently higher N40-P50 peak-to-peak amplitude and greater proportional P50 inhibition. These findings suggest that smokers have greater sensory gating capability as measured by the P50 S2/S1 suppression. Thus, it was a chronic effect that was not impacted by abstention. This is taken as support for hypothesized increased inhibitory activity of dopamine due to MAO inhibition.

MAVA analysis of the P50 data, using 20 msec post-stimulus time windows, showed sensory gating results similar to those reported above. Specifically, GBO sensory gating was observed as starting at either 20 or 40 msec and lasting to 80 or 100 msec. across groups. Furthermore, smokers demonstrated greater GBO sensory gating than did never-smokers. These findings provide corroboration to the P50 results and validation of the utility of MAVA analysis.

In the oddball paradigm, regardless of abstaining or smoking, smokers showed a shorter MMN latency than never-smokers. MMN latency is sensitive to the difference between the standard stimuli and the oddball stimuli; the greater the difference, the

shorter the latency. These data suggest that the smokers had greater perceptual acuity. Such acuity may provide greater selectivity of attention to stimuli, and therefore be an effect in parallel with sensory gating.

MAVA analyses of the transient 40 Hz response showed both group main effects and a condition by group interaction. Smokers showed greater activation regardless of condition in frontal and right temporal regions, from 0-20 to 100-120 msec post stimulus. The 0-20 msec frontal response showed a condition effect, whereby the smokers showed greater activation in the smoking condition in the left frontal region, but did not differ from non-smokers in the abstaining condition. The smokers' greater right temporal activation at 100-120 msec may reflect greater auditory tone difference processing, supporting the hypothesized greater perceptual acuity among smokers. The greater frontal response is congruent with the results obtained from the paired-pulse task. These findings are seen as being consistent with the hypothesized greater chronic dopaminergic activity due to MAO inhibition. The condition X group interaction seen in the left frontal region in the first 20 msec is proposed as possibly reflecting an early response activation in the left frontal reward system. This finding may reflect the short-acting GABAergic action of nicotine on the inhibitory interneurons that produced this response.

Goals of Research and Formal Hypotheses

The goals of this research were to verify our earlier observations in heavy smokers under conditions of abstaining and smoking. They were administered the same experimental procedures as employed previously (Crawford et al., 2002; McClain-Furmanski, in preparation) with the exception of their being presented either a denicotinized cigarette or a cigarette with a known does of nicotine, rather than their own cigarette to smoke.

This approach was designed to test a question that was unanswerable in the prior studies: Were the condition differences noted in the smokers due to nicotine or some other chemical or cognitive effect? While denicotinized cigarettes do not produce EEG

changes normally associated with nicotine (Robinson et al., 2000), smokers do find smoking denicotinized cigarettes more satisfying and rewarding than abstention, possibly due to the sensorimotor aspects associated with the act of smoking per se (Rose et al., 2000). Thus, the possibility remained that we might find activation of the reward system in the absence of nicotine.

The formal hypotheses for the two studies in the present research are provided below.

Study 1: Oddball Paradigm, Transient 40 Hz Response

1. In the nicotine group, the transient 40 Hz response would increase after smoking in the first time window (0 to 20 msec).

2. For the denicotinized group, two alternative hypotheses were assessed.
   (a) No changes, or a decrease in the early transient 40 Hz response after smoking would be taken as evidence that the changes noted in the nicotine group are due to the psychopharmacological action of nicotine.
   (b) An increase in the transient 40 Hz response after smoking would be taken as evidence that the changes noted are due to the act of smoking, rather than the psychopharmacological action of nicotine.

3. The hypothesized effects noted in 1 and 2 would show a left fronto-central localization.

4. There would be no other differences noted between groups throughout the remainder of the transient 40 Hz response.

Study 2: Paired Pulse, P50 and MAVA

5. There would be a significant reduction in the response to the second stimulus (S2) as compared to the response to the first stimulus (S1), measured as the ratio S2 divided by S1, in the N40-P50 amplitude.

6. There would be no main effects or interactions involving group membership found in the S2/S1 ratio since both were smokers and did not differ in smoking history.

7. The S2/S1 ratio effect would be greatest at FCZ.

8. MAVA analysis of these data would show results similar to the S2/S1 ratio, across more than one of the 20-sec time windows. Due to limited prior evidence in the literature (Crawford et al., 2002), the number of time windows that would be impacted was not delineated.

Although no testable formal hypotheses were put forward, the above results were compared with our prior results with smokers and non-smokers. We expected that both smoker groups in the present work would show chronic (not condition related) effects similar to those of the prior smokers. Furthermore, we expected that the nicotine group, and possibly the denicotinized group, would exhibit acute effects as seen in the prior smokers.

There is a potential confound of withdrawal anxiety in the groups selected for this study. Withdrawal anxiety can be instigated in the absence of withdrawal itself. The subject need merely contemplate withdrawal in order to develop an anxiety state. In as much as we are providing the participants with a cigarette other than their own, they might consider the possibility of lack of desired effect and in so doing bring about such an anxiety state. This would appear as a lack of nicotine related early response differences as put forth in hypotheses 1 through 3. The S2/S1 effects noted in hypotheses

4 through 8 should not be affected, nor would comparison of these effects with those seen in the prior smokers.

Chapter 2: Methods

Participants

Participants were 30 right-handed male smokers, 20 to 29 years of age (M = 22.6), with no known medical or psychiatric problems that could impact the EEG results. Participants were medication free. They had abstained from caffeine for at least 8 hours prior to testing, and from alcohol for at least 48 hours. They had smoked for at least 2 years (M = 5.21; SD = 2.39) and reported smoking at least one pack of cigarettes a day or more for the last year or longer. None reported that they, their parents or their siblings had any psychiatric disorders that might be correlated with sensory gating deficits.

Participants were recruited from a large mid-Atlantic university and the surrounding area via advertising flyers posted on public bulletin boards, radio and newspaper advertising and by posting an announcement on public access internet discussion groups (Usenet). They were paid $30 for their participation.

Six participants were later rejected due to equipment failure, excessive artifacts, or post-data acquisition admission of criteria violation. This resulted in a total of 24 participants, 12 each in groups that received cigarettes with nicotine or denicotinized cigarettes. The participants were not depressed as measured by the Beck Depression Inventory (M = 5.96; SD = 5.07; Beck, 1967).

Cigarette Preparation

Ten Marlboro cigarettes were weighed and their weights averaged (M = 0.95 g). Denicotinized cigarettes and physically identical cigarettes with nicotine were created by a laboratory assistant, using tobacco and a cigarette manufacturing machine provided by the Peters Center for the Study of Parkinson's Disease (Dr. Neal Castagnoli). The nicotinized tobacco was a mixture used to produce Marlboro cigarettes, and thus carried a nicotine delivery of approximately 1.1 mg. The denicotinized tobacco was an identical

mixture that had been treated with super critical carbon dioxide extraction in order to remove the nicotine, and provided less than 0.04 mg of nicotine.

The cigarettes were weighed, and any that did not weigh 0.95 +/- 0.05 g were rejected. The remaining cigarettes were packaged and marked with a code to differentiate them, but the experimenter remained blinded as to which were which until statistical analyses were performed. The key for decoding the groupings were delivered by the laboratory assistant, and were stored in Dr. Crawford's office, with a duplicate stored in Dr. Castagnoli's office. The cigarettes were stored in a refrigerator in order to maintain freshness throughout the experiment.

Procedure

This study, and the informed consent form used, was approved by the Virginia Tech Institutional Review Board.

Phone or e-mail screened potential participants. They were asked whether they had ever had any major medical problems, a head injury, a diagnosis of attention deficit disorder or learning disability, had ever been treated for any other neurological or psychiatric problems, had any hearing problems or were currently taking any medications. Those who denied having any of these were briefed regarding the nature of the experiment and procedure, as well as the payment involved. They were told only that the cigarette that would be provided to them had "a precisely known amount of nicotine." They were not told that the cigarettes would contain a normal dose of nicotine, or none at all. Any respondent that then expressed an interest in participating was recruited and scheduled for testing.

Upon recruitment, participants were instructed to abstain from midnight the night before until the time of testing. They were instructed to refrain from caffeine on the day of testing, and to abstain from using alcohol or other drugs for at least two days prior to testing. They were asked upon recruitment the brand of cigarette they smoked. The

experimenter determined the dose of nicotine provided by that brand using the FTC report "Tar", Nicotine and Carbon Monoxide of the Smoke of 1294 Varieties of Domestic Cigarettes for the Year 1998 (FTC, 2000).

Participants arrived at the lab between 8 and 10 AM, and informed consent was obtained (see Appendix A). They were tested for breath carbon monoxide (CO) levels (Breathco Vitalograph, Lenexa, KS) to verify abstention (M = 9.12; SD = 3.37). Abstention was defined as less than 13 parts per million (ppm) of breath CO (10 ppm limit plus 3 ppm instrument maximum error). Those participants whose breath CO was greater than 13 (N = 3) were retested after completing the questionnaire packet, approximately 1 hour later. Those whose breath CO did not deviate by more than 3 ppm were taken to be abstaining (Jed Rose, personal communication).

The participants filled out a medical screening questionnaire (Appendix B), questionnaires relating to handedness (Annett, 1970), tobacco use (Heatherton et al., 1991; Appendix C), alcohol (Appendix D), drug use (Appendix E) and familial history of schizophrenia (Appendix F). The experimenter, to determine whether participants met all inclusionary criteria evaluated these questionnaires.

A subject number was assigned to each at this time. The numbers were assigned sequentially, from 1 through 30. This was used to separate the participants into groups, according to even or odd participant number. The cigarettes had previously been coded by the laboratory assistant as "O" for Odd (nicotine), and "E" for Even (denicotinized).

All participants were briefed about the nature of the stimuli and tasks, and received a brief (~30 sec of each task) presentation of the stimuli for familiarization. Participants were then fitted with an EEG cap. Vertical EOG electrodes were applied above and below the right eye, horizontal EOG electrodes next to the outer canthus of each eye and reference electrode placed on the nose. The participant then entered the testing room and electrode impedance measured. All testing took place in a sound attenuating, electrically shielded room, with the experimenter in an ajoining room.

Stimulus presentation and EEG recording then began. The stimuli sets for the two studies (described below) were presented as oddball paradigm first (study one), and paired pulse P50 paradigm second (study two). Each presentation lasted approximately 5 minutes. After the first set of tasks, the experimenter asked the participant a set of questions regarding their subjective experience of the stimuli (Appendix G).

Each participant then left the testing room, and was taken outside to the smoking area. The EEG cap was not removed. The selection of which cigarette to give was according to the even/odd participant number. The participants were unaware that there were more than one kind of cigarette.

After smoking the provided cigarette, each participant immediately returned to the testing room, and was reconnected to the EEG. After verification that there was still suitable EEG signal, they were presented with the second set of tasks in the same manner as described above.

After all tasks were completed, the EEG cap was removed. The participants were then asked to fill out other questionnaires relating to other studies being conducted in parallel with this work. Afterwards, the participants were paid, provided a copy of the consent form, provided information about smoking cessation opportunities, and dismissed.

Stimuli and Instructions

Stimulus presentation was controlled by Neuroscan® STIM stimulus generation and presentation control software (Neurosoft Inc., Sterling, VA). Auditory stimuli were presented through a pair of speakers, one on each side of the participant, approximately 75 cm from the participant's ear. Visual stimuli were presented on a 32 cm diagonal computer monitor 80 cm directly in front of the participant.

Study 1: Oddball Paradigm

The modified oddball paradigm consisted of 500 stimuli: 400 were 1000 Hz tones (standard), and 75 were 1200 Hz tones (oddball). These were presented at 70 dB SPL measured at the position of the participant's ear, and were of 50 msec duration including 5 msec rise and fall times. The remaining 25 stimuli were visual checkerboard reversals (novel). Participants were instructed to watch the checkerboard and press a button as fast as they could when it reversed. The visual stimuli were included as an attentional control only, intended to force the subject to maintain vigilance to the visual stimuli and thus ignore the auditory stimuli. The stimuli were presented at a constant 512 msec stimulus onset asynchrony (SOA). They were mixed in a pseudo-random manner, with at least 2 and up to 6 standard stimuli between each oddball or novel.

Study 2: Paired Pulse

The paired pulse P50 paradigm consisted of 50 pairs of 1000 Hz tones of 20 msec duration, 0 rise and fall time, at 70 dB SPL. These were presented with an intrapair SOA of 512 msec and an interpair SOA of 5 seconds. The participants were asked to count the number of pairs of tones to themselves, again as an attentional control.

EEG Recording

Data were recorded using a Neuroscan® 32 channel EEG/ERP workstation running SCAN 4.0 software and SynAmps® EEG bioamplifier. Amplifier analog band pass filters were set to 0.1 high pass and 70 Hz low pass, at a digitization rate of 500 Hz, and a gain of 150, resulting in a digitized voltage resolution of 0.557 μV per least significant bit.

Thirty active data channels and 2 bipolar EOG channels were recorded using an ElectroCap® International 32 channel lycra EEG cap with integral EOG electrodes. The active electrodes were referenced to the nose, and grounded through an electrode directly

between FZ and FCZ. The horizontal EOG electrodes were placed at the outer canthus of each eye, and the vertical EOG electrodes above and below the left eye. Electrode impedance was kept below 5 K ohms.

EEG and EP Processing and Statistical Analyses

To process the EEG and EPs, Neuroscan® SCAN 4.0 software was used. In order to maintain consistency and reduce experimenter bias, all EEG data processing (except visual artifact reduction) was automated, and conducted blindly as to group identification of each participant.

The statistical analyses were also conducted blindly so that the experimenter did not know the nicotine status of the even and odd numbered participants. When all data were reduced and analyzed, the experimenter obtained the data file key in order to correctly identify the group and condition pertaining to the data.

In order to better understand predicted group and/or condition differences at chosen individual sites (Huberty & Morris, 1989; Picton et al., 2000), mixed design analyses of variance (ANOVAs) were conducted. For both the oddball and paired-pulse studies, the following electrode locations were assessed: F3, FZ, F4, FC3, FCZ, FC4, C3, CZ, C4, CP3, CPZ and CP4. In addition, the oddball paradigm study included the following additional electrode locations: FT7, FT8, T7, T8, TP7 and TP8. These latter sites were not assessed in the paired-pulse paradigm due to excessive residual noise after averaging, probably due to muscle tension, in the majority of the participants. Regional localization was accomplished by noting groupings of locations where significant effects were seen. Comparing left/right electrode pairs (e.g. F3 vs. F4) in any case where one or both of them exhibited a significant effect further tested laterality. Larger regional groupings were not tested due to voltage biasing caused by differences in distance from the single-point nose reference. If such groupings had been done, an undesired bias would have been introduced: distal sites would have been weighed more heavily than proximal sites and regional differences would have reflected differences at the distal sites

more so. Topographic mapping was used to verify localizations noted in results, and included all 30 active electrodes. The approach employed for each study is described in the following two sections.

Study 1: Oddball Paradigm, Transient 40 Hz Response

Data Processing. Continuous EEG was epoched from 100 msec prestimulus to 412 msec post-stimulus. Epochs had a linear detrend performed on them to reduce false artifact rejection due to DC drift, and were baselined from 50 msec prestimulus to the time of stimulus. Next, the epochs were submitted to automated artifact rejection (+/- 50 μV at either EOG channel or in FP1, FP2, F7 or F8 was rejected. The epochs were then subjected to visual inspection to verify rejected epochs and remove still evident artifacts in these or any other channels. Furthermore, while scanning for additional EOG artifact, it was noted for each subject at which electrode sites there appeared persistent muscle artifact noise that could falsely contribute to the transient 40 Hz response. These were subsequently excluded from statistical analyses on an individual/electrode basis in order to prevent eliminating an entire epoch due to localized artifact. Exclusionary criteria was if the amplitude of the individual electrode signal in the resulting averages exceeded the standard deviation of the group grand average for that condition at any point between –20 and 160 msec.

Epochs were digitally bandpass filtered from 32 Hz to 48 Hz with a 24 dB per octave roll-off using a two pole Butterworth filter. Averaging was then performed in order to extract the transient 40 Hz response. These averages were rectified and low pass filtered at 32 Hz with 24 dB roll-off to extract the MAVA of the transient 40 Hz response.

The data for the nine 20 msec time windows (-20 to 160 msec) were extracted from the MAVA transformed EPs, by averaging the MAVA amplitude across 10 samples in each window and exporting those data to an ASCII file.

Statistical Analyses. ANOVAs were performed independently for each electrode, within each time window, in a 2 (group) by 2 (condition) design. Significant interactions were followed up by paired and independent samples t-tests. Furthermore, where significant results were noted, a 2 (group) by 2 (condition) by 2 (hemisphere) ANOVA was performed on corresponding left/right electrode pairs, with follow up t-tests where appropriate. Results were considered significant at $p < .05$.

Study 2: Paired Pulse P50

Data Processing: Continuous EEG was epoched from 50 msec prestimulus to 462 msec post-stimulus. Epochs were linear detrended, baselined across the 50 msec prestimulus period, and subjected to automatic artifact rejection and subsequent visual inspection as described above.

The epochs were high pass filtered at 10 Hz to remove the non-linear confounding effect of the slow component contributing to the N100 and P200, and averaged. These averages were sorted according to first or second pulse. The P50 was defined as the positive peak between 45 and 75 msec. For each subject, condition and pulse (S1/S2), P50 amplitude was taken as the peak-to-peak amplitude from the preceding negativity (N40).

The epochs were digitally bandpass filtered from 32 Hz to 48 Hz and averaged, then exported as an ASCII file, and transformed into MAVA averages in the same manner as in study one, with the same time windows.

Statistical Analyses. ANOVAs were performed independently for each electrode in each time window, in a 2 (group) by 2 (condition) by 2 (stimulus: S1, S2) design. Significant interactions were followed up by reduced design ANOVAs, and by paired and independent samples t-tests. Furthermore, where significant results were noted, a 2 (group) by 2 (condition) by 2 (hemisphere) ANOVA was performed on corresponding

left/right electrode pairs, with follow up ANOVAs and t-tests as appropriate. Results were considered significant at $p < .05$.

Chapter 3: Results

The results for the two studies are presented separately below. The accompanying tables present a summary of all significant ANOVAs and a breakdown of the complex interactions with follow-up analyses. Since these Fs and ts are not redundantly presented in the text, the reader is referred to the tables. Means and standard deviations for significant analyses are presented in the table as well.

Results for Study 1: Transient 40 Hz MAVA

All sites except F3 and TP8 produced significant effects at some point between –20 and 120 msec. However, in follow up testing of non-midline sites, no left/right differences were found. Although there were no differences found at any site from 0 to 40 msec, this should be viewed in light of the fact that there were significant effects noted pre-stimulus. No significant effects were found after 120 msec. The complete time series of both groups responses at FCZ are given in Figure 4. Figure 5 provides comparison with our prior smokers and non-smokers.

Transient 40 Hz MAVA: Baseline (-20 to 0 msec)

At four right hemisphere locations (FC4, C4, CP4, FT4) there were significant interactions between condition and group (See Table 1). During the prestimulus baseline, the nicotinized group showed a significant decrease in 40 Hz activity at FC4 and CP4 following smoking. For unknown reasons, the two groups differed during abstention condition at FC4, CP4 and FT8.

Table 1. Transient 40 Hz MAVA: Baseline (-20 to 0 msec)

(a) ANOVA Summary

Site	Effect	F =	p =	Follow up analyses			Explanation
FC4	CxG	8.22 $_{(1,20)}$	.010	Condition:	A	$t_{(21)} = 2.48$, p = .021	N > D
					B	n.s.	
				Group:	N	$t_{(11)} = 2.61$, p = .026	A > B
					D	n.s.	
C4	CxG	4.39 $_{(1,20)}$	.049	Condition:	A	n.s.	
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	
CP4	CxG	5.30 $_{(1,20)}$	.032	Condition:	A	$t_{(21)} = 2.26$, p = .035	N > D
					B	n.s.	
				Group:	N	$t_{(10)} = 2.33$, p = .042	A > B
					D	n.s.	
FT8	CxG	6.16 $_{(1.18)}$	.023	Condition:	A	$t_{(19)} = 2.36$, p = .029	N > D
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	

(b) Means and Standard Deviations for Interactions

			Nicotine		Denicotinized	
Site	Effect	Condition	Mean	s.d	Mean	s.d.
FC4	CxG	A	.078	.038	.044	.021
		B	.042	.022	.052	.024
C4	CxG	A	.071	.032	.056	.032
		B	.046	.031	.062	.032
CP4	CxG	A	.073	.024	.049	.029
		B	.044	.035	.055	.032
FT8	CxG	A	.083	.050	.038	.024
		B	.049	.033	.066	.047

Abbreviation key:
Effects: C = Condition; G = Group; H = Hemisphere (L = left; R = right)
Conditions: A = Abstaining; B = After Smoking
Groups: N = Nicotine; D = Denicotinized

Transient 40 Hz MAVA: 0 to 20 msec

There were no significant main effects or interactions.

Transient 40 Hz MAVA: 20 to 40 msec

There were no significant main effects or interactions.

Transient 40 Hz MAVA: 40 to 60 msec

During the 40 to 60 msec time window, unexpected group main effects emerged at C3, CZ, C4, FT7 and TP7 (see Table 2). In all cases, the nicotine group showed greater activity across conditions.

Table 2. ANOVA Summary for Transient 40 Hz MAVA: 40 to 60 msec

Site	Effect	F =	p =	Main Effect Means		Explanation
C3	G	$4.51_{(1,18)}$	.048	N = .161 (.151)	D = .082 (.032)	N > D
CZ	G	$5.63_{(1,20)}$	.028	N = .166 (.108)	D = .098 (.040)	N > D
C4	G	$4.65_{(1,20)}$	.043	N = .169 (.152)	D = .089 (.047)	N > D
FT7	G	$5.45_{(1,18)}$	.031	N = .137 (.094)	D = .067 (.037)	N > D
TP7	G	$6.27_{(1,18)}$	.022	N = .201 (.159)	D = .089 (.046)	N > D

Abbreviation key:
Effects: C = Condition; G = Group; H = Hemisphere (L = left; R = right)
Conditions: A = Abstaining; B = After Smoking
Groups: N = Nicotine; D = Denicotinized

Transient 40 Hz MAVA: 60 to 80 msec

The unexpected group effects continued and spread during the 60 to 80 msec time window (see Table 3). Of the locations, only F3 and CP4 did not exhibit this main effect. Again, the nicotine group showed greater response than the denicotinized group.

Table 3. ANOVA Summary for Transient 40 Hz MAVA: 60 to 80 msec

Site	Effect	F =	p =	Main Effect Means		Explanation
FZ	G	5.30 $_{(1,20)}$	.032	N = .195 (.128)	D = .115 (.047)	N > D
F4	G	7.30 $_{(1,19)}$	.014	N = .179 (.129)	D = .087 (.037)	N > D
FC3	G	5.36 $_{(1,19)}$	.032	N = .183 (.161)	D = .086 (.056)	N > D
FCZ	G	5.54 $_{(1,20)}$	.029	N = .206 (.138)	D = .112 (.052)	N > D
FC4	G	8.09 $_{(1,20)}$	.010	N = .190 (.143)	D = .084 (.041)	N > D
C3	G	9.11 $_{(1,18)}$	.007	N = .178 (.130)	D = .067 (.035)	N > D
CZ	G	5.82 $_{(1,20)}$	.026	N = .190 (.134)	D = .095 (.060)	N > D
C4	G	5.99 $_{(1,20)}$	.024	N = .185 (.145)	D = .085 (.047)	N > D
CP3	G	6.65 $_{(1,19)}$	.018	N = .162 (.116)	D = .074 (.031)	N > D
CPZ	G	4.37 $_{(1,20)}$	.050	N = .165 (.128)	D = .084 (.059)	N > D
FT7	G	7.14 $_{(1,18)}$	.016	N = .132 (.090)	D = .053 (.029)	N > D
TP7	G	9.07 $_{(1,18)}$	.008	N = .197 (.130)	D = .079 (.027)	N > D

Abbreviation key:
Effects: C = Condition; G = Group; H = Hemisphere (L = left; R = right)
Conditions: A = Abstaining; B = After Smoking
Groups: N = Nicotine; D = Denicotinized

Transient 40 Hz MAVA: 80 to 100 msec

The group main effects, with the nicotine group greater than the denicotinized group, continue at F4 and TP7 (see Table 4).

Table 4. ANOVA Summary for Transient 40 Hz MAVA: 80 to 100 msec

Site	Effect	F =	p =	Main Effect Means		Explanation
F4	G	$5.71_{(1,19)}$	.027	N = .115 (.053)	D = .080 (.031)	N > D
TP7	G	$7.96_{(1,18)}$	.011	N = .148 (.087)	D = .082 (.036)	N > D

Abbreviation key:
Effects: C = Condition; G = Group; H = Hemisphere (L = left; R = right)
Conditions: A = Abstaining; B = After Smoking
Groups: N = Nicotine; D = Denicotinized

Transient 40 Hz MAVA: 100 to 120 msec

During the 100 to 120 msec time window, a condition by group interaction occurred at T7 and T8 (see Table 5). Follow up analyses showed this was due to a decrease in activity across condition in the denicotinized group, and an increase in the nicotine group. At T7, the effect was based on a significant decrease in the denicotinized group, and at T8 to a significant difference between the group in the second condition.

Table 5. Transient 40 Hz MAVA: 100 to 120 msec
(a) ANOVA Summary

Site	Effect	F =	p =	Follow up analyses			Explanation
T7	CxG	$5.14_{(1,15)}$	.039	Condition:	A	n.s.	
					B	n.s.	
				Group:	N	n.s.	
					D	$t_{(7)} = 3.18$, p = .016	A > B
T8	CxG	$6.40_{(1,16)}$	.022	Condition:	A	n.s.	
					B	$t_{(21)} = 2.16$, p = .042	N > D
				Group:	N	n.s.	
					D	n.s.	

(b) Means and Standard Deviations for Interactions

Site	Effect	Nicotine Mean	Nicotine s.d	Denicotinized Mean	Denicotinized s.d.
T7	CxG	.097	.058	.074	.036
T8	CxG	.123	.087	.081	.058

Abbreviation key:
Effects: C = Condition; G = Group; H = Hemisphere (L = left; R = right)
Conditions: A = Abstaining; B = After Smoking
Groups: N = Nicotine; D = Denicotinized

Results of Study 2: P50 and MAVA

N40-P50 Peak-to-Peak Amplitude

There was a significant main effect of S1 to S2 reduction at all frontal, fronto-central and central sites (see Table 6). This effect was greatest at FCZ, which is shown in Figure 6. Furthermore, a condition by group interaction occurred at F3 and FC3. At both sites, this was due to greater overall activity in the nicotine group during the first condition only.

There was also a laterality interaction effect at F3/F4. In the second condition, the nicotine group showed greater activation at F4, while the denicotinized group should greater activation at F3. S1 to S2 reduction is given as the ratio of S2 divided by S1 (S2/S1).

Table 6. ANOVA Summary for N40-P50 Peak-to-Peak Amplitude

Site	Effect	F =	p =	Follow up analyses			Explanation
F3	S	13.72 $_{(1,22)}$	.001				S2/S1 = .764
	CxG	4.98 $_{(1,22)}$	.036	Condition:	A	$t_{(22)} = 2.84$. p = .010	N > D
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	
FZ	S	33.57 $_{(1,22)}$	<.001				S2/S1 = .658
F4	S	15.88 $_{(1,22)}$	.001				S2/S1 = .709
F3/4	CxHxG	10.78 $_{(1,22)}$	.003	Condition:	A	n.s.	
					B	n.s.	N: R > L
							D: L > R
FC3	S	9.11 $_{(1,22)}$	.006				S2/S1 = .796
	CxG	4.38 $_{(1,22)}$	.048	Condition:	A	$t_{(22)} = 2.28$, p = .036	N > D
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	
FCZ	S	33.82 $_{(1,22)}$	<.001				S2/S1 = .632
FC4	S	9.53 $_{(1,22)}$	.005				S2/S1 = .770
C3	S	4.51 $_{(1,22)}$	.045				S2/S1 = .832
CZ	S	18.35 $_{(1,22)}$	<.001				S2/S1 = .666
C4	S	6.87 $_{(1,22)}$	.016				S2/S1 = .782

Abbreviation key:
Effects: C = Condition; G = Group; S = Stimulus (S1>S2);
H = Hemisphere (L = left; R = right)
Conditions: A = Abstaining; B = After Smoking
Groups: N = Nicotine; D = Denicotinized

P50 MAVA

S1 to S2 reduction of 40 Hz activity within each time window is given as the ratio of S2 divided by S1 (S2/S1). Unlike study 1, this study showed no prestimulus differences between the nicotine and denicotinized groups. Also, evoked effects were noted earlier, in the 20 to 40 msec time window, and resolved earlier, before 100 msec. Furthermore, an S2/S1 stimulus suppression effect was seen at one centro-parietal site, which was not seen in the N40-P50 analysis. S2/S1 suppression was evident at one or more sites from 40 to 100 msec. No significant effects were found after 100 msec. The complete time series for both groups is given in Figure 7, with our prior smokers and non-smokers included as Figure 8.

P50 MAVA: Baseline (-20 to 0 msec)

There were no significant main effects or interactions.

P50 MAVA: 0 to 20 msec

There were no significant main effects or interactions.

P50 MAVA: 20 to 40 msec

During this time window, three left hemisphere sites (F3, FC3 and C3) showed significant condition by group interactions (see Table 7). In all cases, this was due to a decrease in response in the nicotine group across conditions, while the denicotinized group showed an increase across conditions. Both mid frontal (F3, F4) and central (C3, C4) regions exhibited a condition by hemisphere by group interactions. At the mid-frontal region, this was due to differences across condition in the denicotinized group. In the first condition the denicotinized group had greater activity at F4, while they exhibited greater activity at F3 during the second condition. In the central region, the nicotine group showed greater activation at C4 in both conditions, while the denicotinized group, during both conditions, showed greater activity at C3.

Table 7. P50 MAVA: 20 to 40 msec

(a) ANOVA Summary

Site	Effect	F =	p =	Follow up analyses			Explanation
F3	CxG	6.38 $_{(1,22)}$	.019	Condition:	A	n.s.	
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	
F3/4	CxHxG	7.18 $_{(1,22)}$	.014	Group:	N	n.s.	
					D	$F_{(1,11)} = 6.00$, p = .032	A: R > L B: L > R
				Condition:	A	n.s.	
					B	n.s.	
FC3	CxG	6.76 $_{(1,22)}$	.016				
C3	CxG	7.22 $_{(1,22)}$	.013	Condition:	A	n.s.	
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	
C3/4	CxHxG	4.84 $_{(1,22)}$	.039				
				Condition:	A	n.s.	
					B	n.s.	
				Group:	N	n.s.	A: R > L B: R > L
					D	n.s.	A: L > R B: L > R

(b) Means and standard deviations for interactions

				Nicotine		Denicotinized	
Site	Effect	Condition	S2/S1	Mean	s.d.	Mean	s.d
F3	CxHxG/CxG	A		.266	.112	.137	.098
		B		.214	.181	.273	.267
F4	CxHxG	A		.255	.231	.180	.102
		B		.270	.255	.216	.174

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(b) Means and standard deviations for interactions (continued)

Site	Effect	Condition	S2/S1	Nicotine Mean	Nicotine s.d.	Denicotinized Mean	Denicotinized s.d
FC3	CxG	A		.279	.208	.275	.149
		B		.229	.176	.244	.271
C3	CxHxG/CxG	A		.260	.184	.183	.134
		B		.231	.170	.284	.264
C4	CxHxG	A		.294	.247	.172	.091
		B		.296	.208	.194	.126

Abbreviation key:
Effects: C = Condition; G = Group; S = Stimulus (S1>S2);
H = Hemisphere (L = left; R = right)
Conditions: A = Abstaining; B = After Smoking
Groups: N = Nicotine; D = Denicotinized

P50 MAVA: 40 to 60 msec

In the 40 to 60 msec time window, all frontal, fronto-central and central sites, plus CPZ and CP3 showed significant effects (see Table 8). F3, FC3, C3, CZ, CP3 and CPZ exhibited condition by group interactions similar to those seen in the previous time window. All these sites except F3 and CP3 also showed significant S2/S1 suppression effects.

In laterality testing, only F3/F4 and CP3/CP4 yielded interactions. There was a condition by group by hemisphere interaction at F3/F4. In the first condition, F3 was greater in the nicotine group, while F4 was greater in the denicotinized group. In the second condition, these effects were reversed, with the nicotine group greater at F4 and the denicotinized group greater at F3. There was a hemisphere by group interaction at CP3/CP4. Regardless of condition, the nicotine group showed greater activity at CP4, while the denicotinized group was greater at CP3.

Table 8. P50 MAVA: 40 to 60 msec
(a) ANOVA Summary

Site	Effect	F =	p =	Follow up analyses			Explanation
F3	CxG	6.31 $_{(1,22)}$	.020	Condition:	A	n.s.	
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	
FZ	S	6.85 $_{(1,22)}$	.016				S2/S1 = .786
F4	S	4.81 $_{(1,22)}$	.039				S2/S1 = .829
F3/4	CxHxG	7.10 $_{(1,22)}$	.014	Condition:	A	n.s.	N: L > R D: R > L
					B	n.s.	N: R > L D: L > R
				Group:	N	n.s.	
					D	n.s.	
FC3	S	5.78 $_{(1,22)}$	.025				S2/S1 = .774
	CxG	5.73 $_{(1,22)}$	.026	Condition:	A	n.s.	
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	
FCZ	S	11.25 $_{(1,22)}$	.003				S2/S1 = .729
FC4	S	6.13 $_{(1,22)}$	.021				S2/S1 = .826
C3	S	5.68 $_{(1,22)}$	.026				S2/S1 = .756
	CxG	5.50 $_{(1,22)}$	.028	Condition:	A	n.s.	
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	
CZ	S	9.18 $_{(1,22)}$	.006				S2/S1 = .726
	CxG	6.26 $_{(1,22)}$	.020	Condition:	A	n.s.	
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	
C4	S	4.54 $_{(1,22)}$	.044				S2/S1 = .842

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ANOVA Summary for P50 MAVA: 40 to 60 msec (continued)

Site	Effect	F =	p =	Follow up analyses			Explanation
CP3	CxG	7.30 $_{(1,22)}$	.013	Condition:	A	n.s.	
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	
CPZ	S	4.51 $_{(1,22)}$	.045				S2/S1 = .797
	CxG	5.82 $_{(1,22)}$	.025	Condition:	A	n.s.	
					B	n.s.	
				Group:	N	n.s.	
					D	n.s.	
CP3/4	HxG	5.45 $_{(1,22)}$	.029	Group:	N	n.s	R > L
					D	n.s	L > R

(b) Means and standard deviations for interactions

Site	Effect	Condition	S2/S1	Nicotine Mean	Nicotine s.d.	Denicotinized Mean	Denicotinized s.d
F3	CxHxG/CxG	A		.341	.183	.206	.076
		B		.286	.184	.308	.241
F4	CxHxG	A		.304	.191	.220	.109
		B		.319	.267	.250	.141
FC3	CxG	A		.358	.213	.221	.139
		B		.287	.172	.326	.303
C3	CxG	A		.328	.216	.215	.148
		B		.250	.161	.302	.271
CZ	CxG	A		.342	.185	.231	.142
		B		.265	.150	.256	.115
CP3	CxG	A		.302	.174	.190	.101
		B		.221	.132	.238	.138
	HxG			.272	.157	.205	.105
CPZ	CxG	A		.311	.183	.202	.108
		B		.234	.132	.208	.102
CP4	HxG			.300	.196	.200	.116

Abbreviation key:
Effects: C = Condition; G = Group; S = Stimulus (S1>S2);
H = Hemisphere (L = left; R = right)
Conditions: A = Abstaining; B = After Smoking
Groups: N = Nicotine; D = Denicotinized

P50 MAVA: 60 to 80 msec

Frontal and fronto-central sites, plus C3 and CZ, continued to exhibit S2/S1 suppression main effects (see Table 9). At F3 and F4, there were stimulus (S2/S1) by group interactions. At both sites, the denicotinized group showed significant S2/S1 suppression, whereas the nicotine group did not. In the F3/F4 comparison, a condition by hemisphere by group interaction emerged, with follow up testing showing the same pattern of differential activation across conditions as was seen in the 40 to 60 msec window.

Table 9. P50 MAVA: 60 to 80 msec

(a) ANOVA Summary

Site	Effect	F =	p =	Follow up analyses			Explanation
F3	S	$6.31_{(1,22)}$	.020				S2/S1 = .835
	SxG	$5.86_{(1,22)}$	.024	Group:	N	n.s.	
					D	$t_{(11)} = 4.16$, $p = .002$	S1 > S2
				S1	n.s.		
				S2	n.s.		
FZ	S	$7.72_{(1,22)}$	.011				S2/S1 = .788
F4	S	$5.11_{(1,22)}$	.034				S2/S1 = .817
	SxG	$6.34_{(1,22)}$	.019	Group:	N	n.s.	
					D	$t_{(11)} = 5.31$, $p < .001$	S1 > S2
F3/4	CxHxG	$6.18_{(1,22)}$	.021	Condition:	A	n.s	
					B	n.s.	
				Group:	N	n.s	A: L > R
							B: R > L
					D	n.s	A: R > L
							B: L > R
FC3	S	$5.76_{(1,22)}$	.025				S2/S1 = .784

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ANOVA Summary for P50 MAVA: 60 to 80 msec (continued)

Site	Effect	F =	p =	Follow up analyses	Explanation
FCZ	S	9.96 $_{(1,22)}$	.005		S2/S1 = .741
C3	S	7.02 $_{(1,22)}$	.015		S2/S1 = .806
CZ	S	9.31 $_{(1,22)}$	.006		S2/S1 = .738

(b) Means and standard deviations for interactions

				Nicotine		Denicotinized	
Site	Effect	Condition	S2/S1	Mean	s.d.	Mean	s.d
F3	SxG		S1	.324	.206	.329	.157
			S2	.322	.167	.223	.156
	CxHxG	A		.348	.177	.238	.151
		B		.297	.196	.314	.163
F4	SxG		S1	.323	.223	.302	.138
			S2	.330	.274	.180	.095
	CxHxG	A		.327	.238	.244	.128
		B		.326	.260	.237	.106

Abbreviation key:
Effects: C = Condition; G = Group; S = Stimulus (S1>S2);
H = Hemisphere (L = left; R = right)
Conditions: A = Abstaining; B = After Smoking
Groups: N = Nicotine; D = Denicotinized

P50 MAVA: 80 to 100 msec

The S2/S1 suppression main effect continues at F3, FZ, FC3, FCZ, CZ and CPZ (see Table 10).

Table 10. ANOVA Summary for P50 MAVA: 80 to 100 msec

Site	Effect	F =	p =	Follow up analyses	Explanation
F3	S	11.44 $_{(1,22)}$	.003		S2/S1 = .792
FZ	S	7.63 $_{(1,22)}$	.011		S2/S1 = .820
FC3	S	8.31 $_{(1,22)}$	.009		S2/S1 = .776
FCZ	S	10.58 $_{(1,22)}$	.004		S2/S1 = .778
CZ	S	11.18 $_{(1,22)}$	.003		S2/S1 = .753
CPZ	S	4.90 $_{(1,22)}$	.038		S2/S1 = .826

Abbreviation key:
Effects: C = Condition; G = Group; S = Stimulus (S1>S2);
H = Hemisphere (L = left; R = right)
Conditions: A = Abstaining; B = After Smoking
Groups: N = Nicotine; D = Denicotinized

P50 MAVA: 100 to 120 msec

There were no significant main effects or interactions.

Post-hoc Qualitative Analyses

Although arriving too late to be formally incorporated into the present work, our laboratory recently obtained two new analysis software packages that have provided us with exciting possibilities in extending our analyses to better characterize the results presented here. These are employed here to provide post-hoc qualitative analyses, in

order to offer corroboration of some of the hypotheses, and to validate the MAVA analysis technique.

Source Localization

We have recently installed the Neuroscan® source localization program, SOURCE, and used it to observe the localization of the P50 suppression effect. A grand average EP of all subjects and conditions, based on the difference between S1 and S2 (subtraction scores of S1 amplitude – S2 amplitude) was created from the paired pulse paradigm data.

When examined in a traveling dipole model, the dipole of the S2/S1 effect appeared to emerge at approximately 40 msec in the mid-cingulate, and travel forward to the anterior cingulate until approximately 80 msec. Thus, the failure to fully support the hypotheses regarding localization at FCZ could be due to the fact that the time series analysis in the present work is sensitive to temporally extended phenomena whereas the traditional average EP analysis is not. This possibility can be further examined and re-evaluated using this technique.

Continuous Wavelet Transform: Time-Frequency Mapping

Also, we have recently installed BrainVision® (Brain Products GmbH, Munich, Germany), an advanced EEG analysis package that includes a continuous wavelet analysis module, producing time-frequency mapping of EEG/EP data. A question was raised by Pfurtscheller's lab to Helen Crawford (personal communication, May 2001) as to whether the bandpass filtering used in creating the MAVA results artifactually created the oscillation we have taken to be the transient 40 Hz response.

The method used by their laboratory to determine whether there does in fact exist a significant differences in event related synchronization is based on spectral analysis of particular frequency bands of the signal. Unfortunately, as noted previously, the spectral

resolution of an FFT is sensitive to the number of samples used in the calculation. The number of samples within the response of interest here was, to the closest power of 2 (a necessity for FFT calculation) 64 samples (128 msec), providing no better than an 8 Hz frequency resolution.

Using the BrainVision® wavelet transform module on unfiltered EPs from the transient 40 Hz paradigm, we have been able to show that the oscillatory activity is bounded in the time domain between 0 and 120 msec, but also bounded in the frequency domain between approximately 30 and 50 Hz. Again, although too late to include as a formal testing technique, we express confidence that the signal of interest here, the transient 40 Hz response, and the suppression seen in this response in paired pulse testing, is in fact a real phenomenon. This result is provided as Figure 9.

Chapter 4: Discussion

Overview of Major Findings for Both Studies

The first study assessed the potential differential impact of nicotinized and denicotinized cigarette smoking on the transient 40Hz during the oddball paradigm. Contrary to expectations and to our previous work (McClain-Furmanski et al., in preparation), after smoking, the nicotine group did not show the hypothesized increased transient 40 Hz response in the first 20 ms interval following the auditory stimuli. Rather, after smoking, they showed a decreased 40 Hz activity in the pre-stimulus baseline. Thus, hypothesis 1 was not supported. However, because there was a smoking-related response, an alternative explanation is put forth below, based on the same theoretical background as the hypothesis.

Contrary to expectation, the denicotinized group did show an increase in the transient 40 Hz response after smoking, but this occurred in the prestimulus baseline period and only in the right hemisphere (right lateral FT8, fronto-central FC4, central C4, centro-parietal CP4), two factors which were not incorporated into the hypotheses. Thus, we cannot differentiate between hypothesis 2(a) and 2(b). These effects did not match the expected left fronto-central localization. Thus, hypothesis 3 was not supported. Similarly, an unexpected group main effect occurred with the nicotine group generating significantly more 40 Hz activity (40 - 100 ms) in both abstaining and smoking conditions. This is contrary to hypothesis 4.

In the second study the potential differential impact of nicotinized and denicotinized cigarette smoking on sensory gating and the underlying transient 40Hz response during the paired-pulse paradigm was assessed. Hypotheses 5 and 7 were supported by the data. As anticipated, there was a significant S2/S1 main effect observed at all frontal, fronto-central, and central sites. The midline fronto-central site (FCZ) exhibited the greatest sensory gating as assessed by S2/S1 ratios. While prior research has often reported the central site to be the highest, these findings are in agreement with

Crawford et al. (2002). Hypothesis 6 was not supported, as there were two left hemisphere fronto-central sites (F3, FC3) that exhibited a condition by group interaction.

A significant S2/S1 effect was observed during three time windows (40 – 100 msec) in fronto-central regions of both hemispheres. Thus, hypothesis 8 was supported.

In the following sections, each of the studies is discussed in further detail.

Study 1: Oddball Paradigm, Transient 40 Hz

In preliminary analysis, prior to decoding the group membership, it was noted that several channels, particularly those around the periphery, contained significant muscle artifact. In as much as it was crucial to accurately characterize the transient 40 Hz response, problematic signals were excluded from analysis. The original recordings were re-examined. Sites and conditions in which individuals showed excessive noise in the signal were noted and then eliminated from the data set prior to statistical testing.

We also noted a strong group effect where none should have occurred. We re-examined the original recordings and found that several individuals in the odd-numbered (nicotine) group exhibited much greater response overall. However, this occurred in the absence of significant noise confounds. The data were examined with and without these individuals included in statistical testing. Although the magnitude of the group differences changed, the nature of the other results did not. Thus, it was decided to retain these participants' data.

In the present study, a smoking related increase in the transient 40 Hz response during the first 20 msec post-stimulus was not observed, as was hypothesized. In our earlier work (McClain-Furmanski et al., in preparation), a smoking related increased in the transient 40-Hz response was observed. Thus, in the present study, the 1.1 mg nicotine dose level did not replicate observed prior findings with an individual's own cigarette (often of less nicotine level than that of the 1.1 mg level). Whether dose level

may have had an impact is not known, yet in the literature it can have an influence (e.g., Pritchard, 1991).

However, this finding should be considered in light of the unexpected interactions that occurred in the –20 to 0 msec period just prior to the stimulus. During the pre-stimulus 20 msec baseline window, there was a significant interaction between condition and group. This was unexpected, but perhaps congruent with the hypothesized drug motivation model. When smoking a nicotine containing cigarette, there was a decrease in activation in the right fronto-centro-parietal region (FT8, FC4, C4, CP4), suggestive of greater relative left hemisphere reward motive relative to decreased right hemisphere avoidance motive. Those abstaining individuals who smoked a cigarette without any appreciable nicotine showed a further increase in right activation, potentially reflecting a greater avoidance motive with continuing abstaining. In as much as the expected response was thought to be a biasing of the response due to smoking and/or nicotine, which is apparent regardless of the presence of the stimulus, it remains possible that this biasing may be visible in the pre-stimulus period. It was not noted in our prior work. Since this time period is approximately 500 ms after the previous stimulus, it may still be influenced by the prior stimulus and is therefore not a true baseline. Further work needs to assess if the effect is present for a longer pre-stimulus period of time than 20 msec pre-stimulus.

There was an unexpected condition by group interaction between 100 and 120 msec at bilateral temporal regions (T7, T8) that did not continue into the 120 to 160 msec period. During abstaining neither group differed in 40 Hz activity level, but during the smoking condition they did. While those individuals given nicotine did not change from their prior abstention period, those individuals who did not receive nicotine showed a decrease in 40 Hz activity in both temporal regions, significantly so ($p = .016$) in the left temporal region and in the same direction in the right temporal region. That this effect was localized to the temporal region, it suggests that primary auditory cortex is implicated (Naatanen, 1992). Potentially this suggests that the denicotinized group were in fact reducing their "binding" to, or attention towards, the auditory tone around 100

msec, and returning to pre-stimulus baseline, as the abstaining from nicotine smoking intensified over the experimental session. The 100 to 120 msec time window is associated with the beginning of the time period associated with the fairly automatic discrimination detection period. While our prior work did not show a differential impact of smoking tobacco on the MMN, a recent study by Engeland et al. (2002) suggests that further analyses of the MMN should be conducted in the present data set.

The unexpected group effect between 40 and 100 msec was such that the nicotine group had higher 40 Hz activity across both conditions than did the denicotinized group. As Jones noted in 1986, "individual differences in sensitivity to nicotine may help account for a number of anomalous findings uncovered in research on nicotine regulation" (p. 445). Post-hoc analyses showed no relationships between overall level of gamma band activity response and amount of nicotine present in the participants' normally smoked cigarette. The impact of individual differences in response to smoking have been shown for other physiological measures (Niaura et al., 2001) as well as EEG measures. Not considered in the present study is the potential impact of personality. For instance, Gilbert (1987) noted that personality had an impact on EEG asymmetry following smoking. Since depression may impact EEG activation after smoking (Gilbert, Meliska, Welser, & Estes, 1994), it is important to note that the groups did not differ in depression level, nor were they depressed. Whether smoking is perceived as being arousing or stressful to an individual, in general, may also have an impact on cortical arousal. This was not assessed in the present analyses. These unexpected findings sensitize this researcher to the importance of examining moderating participant characteristics when possible in smoking-related research.

Study 2: Paired Pulse Paradigm, P50 and P50 MAVA

N40-P50 Peak-to-peak

Contrary to expectation, at the right mid frontal (F3) and fronto-central (FC3) sites there were similar condition by group interactions. The amplitude of the N40-P50, across S1 and S2, was greater in the nicotine group during abstaining, possibly due to unknown group differences as discussed previously. After smoking, the nicotine group showed a decrease in amplitude while the denicotinized group showed an increase.

Additionally, there was an unexpected condition by hemisphere by group interaction at the mid frontal (F3, F4) region. During abstaining there was no N40-P50 amplitude differences between groups nor sites. After smoking, the nicotine group showed an increase in N40-P50 amplitude at F4, while the denicotinized group showed greater amplitude at F3. This suggests a nicotine effect of a different nature than was expected. An increased left fronto-central response in the nicotine group after smoking was expected, yet the opposite occurred. After smoking the nicotine group showed greater right activation. It is as if, rather than activating the reward system, the avoidance system is activated, indicating a negative or unpleasant experience.

As noted earlier, while low doses of nicotine have an anxiolytic effect, higher doses have an anxiogenic effect (File et al., 1998). Furthermore, the effects of smoking on hemispheric asymmetry may be influenced by dose level (Pritchard, 1991). The cigarette that was given to the nicotine group contained approximately 1.1 mg of nicotine. Nearly all the smokers in this study smoked light cigarettes, with an average FTC yield of .77 mg according to their self-report of brand smoked. It is possible that the above effects indicate that an overdose effect is being seen. In our earlier work, the smokers all smoked their own brand of cigarette, and no such effect would have emerged.

As predicted, significant sensory gating (S2/S1) was observed at the frontal, fronto-central and central regions with the greatest being at FCZ. This was a chronic

effect observed among the smokers as there was no impact from smoking after the abstaining condition. The lack of a nicotine effect on sensory gating supports our prior work (Crawford et al., 2002).

In the present study, the S2/S1 ratio indicated a 37% S2 suppression. This suppression ratio falls between that observed for smokers and never-smokers in our prior work (Crawford et al., 2002). There we found a 43% suppression for smokers and a 33% suppression for non-smokers at electrode FZ (FCZ was not presented in this publication). It should be noted that the smokers in the present work were substantially younger than were Crawford et al.'s smokers. This age difference may contribute to the ratio differences observed between the two samples. Furthermore, because the sample was younger and from an undergraduate college population, there is a potential impact from marijuana use. It was not able to be determined due to the lack of a urine analysis in the present study. Contrary to cigarette smoking, marijuana has been shown to decrease sensory gating (Patrick et al., 1999; Patrick & Struve, 2000).

It should be noted that the S2/S1 ratios found here, and in our previous work, showed less S2/S1 suppression than what is typically reported in the literature. As stated in our published results (Crawford et al., 2002), this is most likely due to the use of a 5 sec inter-stimulus interval. Fruhstorfer et al. (1970) found that S2/S1 effects could be seen out to 8 sec, a finding we were unaware of during our earlier work. In order to maintain consistency with our prior work, so that direct statistical comparisons of the data could be made, this 5 sec interval was maintained in the present work.

The fact that most of these smokers smoked light cigarettes may have had a bearing on the smaller S2/S1 reduction as compared to the previous results. Light cigarettes have a comparable amount of nicotine to regular cigarettes. However, they are constructed with small holes near the filter, which let in air as the smoker inhales. Thus, all components in the smoke are diluted, including those that might be responsible for MAO inhibition.

P50 MAVA

As hypothesized, there was a significant S2/S1 main effect found from 40 to 100 msec post-stimulus. In contrast to the above discussed N40-P50 results, the most pronounced effect was seen at CZ, and greatest during the 40-60 msec time window, with a 27% suppression. Our previous (Crawford et al., 2002) work found that the greatest S2/S1 effect at FZ occurred during the same 40-60 msec time window in smokers, with a 40% suppression to S2. In this earlier work, the S2/S1 effect was significant between 20 and 80 msec. The range of time windows in which significant S2/S1 effects are noted here are the same as the non-smokers in the previous work. However, the previous non-smokers showed the greatest S2/S1 effect during the 60-80 msec window. Again, these differences from our prior results may be due to the participants' usual choice of cigarette, and/or the younger age of these participants and the subsequent shorter smoking history.

There were condition by group interactions at several sites, between 20 and 60 msec, which were similar to those noted in the oddball task, with a decrease occurring in the nicotine group and an increase in the denicotinized group. Between 20 and 40 msec, these interactions occurred at left fronto-central sites (F3, FC3 and C3). Also during this time window, there were two condition by hemisphere by group interactions, with different patterns of change. At the bilateral mid frontal region (F3, F4), the denicotinized group displayed a greater response at F4 while abstaining, but a greater response at F3 after smoking. This would be consistent with the effect expected in hypothesis 2(b). However, at central region (C3, C4), the nicotine group exhibited a greater response at C4 in both conditions, whereas in both conditions the denicotinized group exhibited greater response at C3.

In the 40 to 60 msec window, the same pattern of condition by group interaction occurred at most of the left and midline sites. In addition, condition by hemisphere by group interactions were seen. At mid frontal region (F3, F4), the denicotinized group changed across condition exactly as they did in the similar interaction in the prior

window, greater at F4 while abstaining and at F3 after smoking. However, the nicotine group changed across conditions in an opposite fashion, being greater at F3 while abstaining, and greater at F4 after smoking. The effect at the centro-parietal (CP3, CP4) in this time window was identical to that observed in the prior time window. The nicotine group had greater response at CP4, and the denicotinized at CP3. While the mid-frontal (F3, F4) differences could be accounted for by the nicotine effect postulated earlier, there is no theoretical basis to account for the central (C3, C4) and centro-parietal (CP3, CP4) interactions in the present work.

During the 60 to 80 msec window, the condition by hemisphere by group effect at mid frontal (F3, F4) is still evident, but the condition by group interactions are not. Instead, during this window, a stimulus by group interaction occurs. At F3 and F4, the denicotinized group continued to exhibit significant S2/S1 reduction, but the nicotine group did not. S1 was similar between the groups. While the S1 response was comparable between the groups, the S2 response in the nicotine group was of the same magnitude as S1, while the S2 response in the denicotinized group remained lower. Because it is not associated with condition, it is possible that this effect is due to the previously noted tendency for some of the nicotine group participants to exhibit greater overall activity. It might be possible that this difference, the tendency to show greater overall activity, is associated with reduced sensory gating over a small portion of the response's time course. Such possible differences can now be tested due to the application of time series analyses such as MAVA as used here. The effect noted here merits further investigation.

Chapter 5: Summary

Conclusions

The hypothesized nicotine effect is not adequately supported by these data. An alternative, that the data reflect a negative affect response to a nicotine overdose, is postulated. However, comparison of the denicotinized group with the prior studies suggests that there was in fact a reward system activation due to smoking in the absence of nicotine. Unfortunately, due to the shortcomings in the nicotine group results, the present work does not produce sufficient evidence to justify making that claim.

The condition by group interaction seen at 100 to 120 msec is interesting in that it localizes to the sites most closely associated with the auditory cortex (T7 and T8), and appears nowhere else. This raises the possibility that other systems, not just the reward system, might be suitable for examination for nicotine effects. In fact, this point may be crucial, as both nicotine and the act of smoking might cause increased response in the left frontal reward system, making it impossible to differentiate them at that region, even with stringent control over nicotine dose.

On the other hand, our prior work on sensory gating as time series analysis is replicated, validating the technique. Although not directly testable, comparison of these results with the earlier results suggests that these smokers too had greater sensory gating than non-smokers, though not by as great a difference as our prior smokers.

These data, taken with our prior work, support the hypothesized MAO inhibition effect. These studies can now be extended to comparisons of these data to MAO activation levels in these and future participants.

The hypothesized localization of the S2/S1 suppression was not formally supported by the resulting means. However, the effect size difference between the noted maximum (at CZ) and the hypothesized maximum (FCZ) was only 3 nanovolts (.726 μV

at CZ; .729 μV at FCZ). Furthermore, the statistical results indicate greater significance at FCZ ($F = 11.25$, $p = .003$) than CZ ($F = 6.26$, $p = .006$). This failure to support the relevant hypotheses must be considered in the light of what was operationalized as the result that would be taken as evidence. Additionally, the source localization performed suggests that the effect is not stationary, but rather moves across the cingulate, and thus would appear at different times to be greatest at CZ or FCZ.

Implications and Future Research

The present work, building upon our prior work, shows the utility of time series analysis of oscillatory activity. Differences in time course are not possible with traditional evoked potential analysis, apart from single-point latency measures. Time series analysis allows the evolution of an oscillation to be examined.

However, the results here also indicate some of the shortcomings of this technique. Amplitude related effects, and differences between these, are better measured by peak amplitude, as opposed to mean amplitude. Furthermore, in studying oscillatory activity, muscle noise artifact can become more of a problem than in traditional analyses. In the future, when feasible, both techniques should be used to compliment each other.

The MAVA technique used in the present study analyzed evoked response to stimuli. In addition, it can be used to examine ongoing, internally directed cognition, by applying MAVA to induced activity in single-sweep EEG data. The pre-stimulus effects noted in the oddball paradigm were post-averaging residual signals and may have represented phenomena better examined in terms of induced activity.

Because the left-frontal reward system may be activated by both nicotine and the act of smoking per se, a different approach than was used in the present study may be necessary. Studies related to smoking cessation, and nicotine studies in non-smokers, utilize nicotine gum or nicotine spray. This would seem to be a better method to use in order to determine if nicotine is responsible for at least part of the hypothesized reward system activation. Comparison of such an effect with that found after smoking

denicotinized cigarettes would be better able to differentiate between these.

The results relating to sensory gating rely on a hypothesized influence of MAO inhibition on this process. While sensory gating is adequately shown here, and MAO inhibition is adequately shown in smokers (e.g. Fowler et al. 1996; Fowler et al. 1998), these should be directly correlated within subjects. The MAO data exists for the participants from the present work. Now that their sensory gating data is available, this work can commence. Positive results from such work could have major implications for the prevention of Parkinson's disease.

No studies exist which examine individual differences in EEG response to smoking. Such work might assist the present work in determining whether the problematic responses found herein represented a phenomenon worthy of further study. Such work needs to be accomplished.

The sensory gating effect is considered a part of auditory processing. However, such an effect might occur in other sensory modalities, and perhaps even in cognitive processing. Studies examining pair-pulse stimuli need to be conducted across modalities within subjects, and tested for correlation between modalities. One such study, comparing auditory and somatosensory processing, is currently under way in our lab.

The term "sensory gating" may be called into question by examination of the various studies that seem to mimic this paired-stimulus effect. Attentional blink, a visually based cognitive system phenomenon, and inhibition of return, a visuo-spatial system phenomenon, both rely on a half second inter-stimulus interval for maximal disturbance in the ability to correctly perceive the second stimulus. It is possible that these, and sensory gating, share a common underlying mechanism. A general system that maintains the orienting response during a time period sufficient to judge an environmental event, and form an appropriate response if necessary, would seem a logical possibility. Within-subjects studies across several modalities and paradigms, particularly with an eye towards individual differences due to factors that would impact the inhibitory systems underlying orienting, are needed.

Time-frequency mapping applied to EEG analysis opens new horizons. Using this technique, the non-linear dynamics of brain activity can be explored directly as the phenomenon itself, rather than in an abstracted sense. This technique, and the non-linear statistical techniques used to test the data, needs further exploration.

Similarly, source localization could be applied to determine what brain structures are associated with the effects found in the present and prior studies. Not only could the hypothesized reward system activation be more reliably determined using this technique, but the intriguing observation of the localization of the S2/S1 sensory gating dipole moving from mid-cingulate to anterior cingulate, could be further investigated. In as much as the anterior cingulate is related to attentional processing (for review, see Duncan and Owen, 2000), such an examination would validate the observation that smoking enhances attention.

A logical next step in the study of smoking effects on sensory gating would be a comparison of ex-smokers to the present and prior work. Determining whether MAO levels and sensory gating effects return to levels found in never-smokers would lend evidence to the hypothesized MAO inhibition effect. Furthermore, if this were done concurrently, or in parallel, with individuals undergoing smoking cessation, it could be determined whether changes in MAO and sensory gating effects correlate across time.

Finally, and most importantly, our present and prior work, taken with examinations of MAO levels in the participants, validate the continued search for the constituents of tobacco, and possibly other substance, responsible for the effects noted. Such substances may prove to be neuroprotective factors that could lead to pharamceuticals used to prevent Parkinson's disease and possibly other neurodegenerative diseases, and thus have a profound impact on the lives of millions of people. Furthermore, by knowing what substances serve as neuroprotective factors, we would be better able to determine what biochemical markers to look for in individuals in order to find those more predisposed to neurodegenerative diseases, and therefore target them as more needful of these potential pharmaceuticals.

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Appendix A: Consent Form

Title of Experiment: Auditory Evoked Potentials in Smokers

This study examines the changes in brain waves of smokers for evidence of activity related to nicotine, and for evidence of another substance in tobacco thought to prevent Parkinson's Disease. Specifically, it examines changes in the brain's responses to auditory tones presented at approximately 70 dB.

Procedure

Participants are asked to abstain from smoking overnight and up until the time of testing (at least 8 hours) and will be tested with a carbon monoxide monitor to verify that they haven't smoked. You will also be asked to fill out some questionnaires regarding your health history, tobacco, alcohol and drug use. These will be examined immediately in order to determine if you have had any conditions that would influence the results. If you haven't smoked since the previous night and have no medical conditions that might cause problems, you will be allowed to continue.

You are to notify the experimenter immediately if you have ever had an allergic reaction or rash to any skin lotions. We use a commonly available cosmetic skin cleanser to get better recordings. Very rarely a person has a reaction to this cleanser.

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 merely measure, they do not produce any electricity. We will also place small electrodes on your face to measure eye blinks. To protect you from infection, the cap and electrodes will have been disinfected by the experimenter prior to your arrival. An elastic band around your chest helps hold the cap tightly on your head. This may be slightly uncomfortable. If so, we can adjust it.

You will be tested first before smoking.

You will sit in a sound-attenuating room, much like a hearing test booth. There will be a computer screen in front of you, and there will be a speaker behind your head. We will be recording your brain waves during three tasks.

In the first task, you will see a checkerboard on the screen with a red dot in the center. You are to watch this for an occasional reversal (black goes white and vice versa). When you see that, you are to press the button that will be provided. This is a reaction time test, so it is important that you watch closely and push the button as fast as possible. There will also be tones coming from the speaker about every half second. Most will be the same, but a few will be a different pitch. You are to ignore these, and just focus on the screen. The red dot in the center is for you to keep your eyes focused on. We are trying to minimize your eye movements, as they change the recordings of the brain waves. This task will last approximately 5 minutes.

In the second task you will see a black screen with a crosshair (plus sign) in the middle of the circle. Again, this is for you to focus your eyes on, to minimize eye movement. You will hear pairs of tones, always of the same pitch. These will be about a half second apart. Then after 5 or 10 seconds, there will be another pair of tones. This will continue for approximately 5 minutes. Your task is to simply pay attention to the tones and count them.

The third task is identical to the second, except that clicks will be used instead of beeps.

After both tasks you will be asked a few questions about how the tones sounded, etc. Then you will be taken outside to smoke while wearing the cap. (It takes a long time to get the cap on you, and we don't want to hold you up). You will be given a cigarette with a precisely known amount of nicotine, but no more than the average amount of nicotine in cigarettes in the US (according to the FTC report on US brand name cigarettes). After smoking you will be taken back into the testing room, and will be given the same tasks in the same order. Afterwards, you will be asked the same questions about what the tones

sounded like. Then you will be paid and may leave. You may also see your recorded brain waves, and ask about the nature of the research if you wish.

You will then be asked to have blood drawn. The consent form for this is attached.

The total time for the experiment is expected to be 2 hours.

ANONYMITY AND CONFIDENTIALITY OF RESULTS

The results of this study will be kept strictly confidential. At no time will the experimenter release any information which would identify you. You will be assigned a code number which will be used on all data. Results presented will only identify groups (smokers, non-smokers, etc.), not individuals. The only time this confidentiality could be broken is in the case of a medical or psychiatric emergency, at which time the experimenter would contact the appropriate agency.

DISCOMFORTS AND RISKS

There are minimal risks to you in this study. The EEG device is constructed in such a way that no electricity can come from it to you. When you smoke, you may experience dizziness or other symptoms. Since you are a regular smoker, you will probably not experience this. You will not be given more than your accustomed dose of nicotine. If at any time during the study you feel you are in need of medical attention, you are to notify the experimenter immediately.

BENEFITS OF THIS PROJECT

No personal benefit beyond recompense is promised you. Your participation will help advance knowledge of how brain systems work, and how smoking influences those systems. The results obtained will be compared with that obtained from non-smokers.

PARTICIPATION AND COMPENSATION

Participation is voluntary. You are free to withdraw at any time. You will receive $30 for your participation in the two parts of the study (brain wave and blood draw).

USE OF RESEARCH DATA

The information obtained from this study may be presented at scientific meetings or in articles in scientific journals, or used for any purpose that the Virginia Tech Department of Psychology considers to be proper and in the best interest of education or research.

APPROVAL OF RESEARCH

This project has been approved by the Human Subjects Committee of the Department of Psychology and by the Institutional Review Board of Virginia Tech. You will receive a copy of this consent form, with contact information for the persons who oversee research conducted on human subjects. If at any time you feel you have been mistreated, you are invited to contact them.

PARTICIPANT'S PERMISSION

I have read and understand the above description of the study. I have had an opportunity to ask questions and have them all answered. I hereby acknowledge the above and give my voluntary consent for participation in this study. I further understand that I may withdraw at any time without penalty. I understand that if I have any question regarding this research and its conduct, I should contact any of the persons below:

Primary Research: Dennis McClain-Furmanski, 231-6581, 381-8538, dmcclain@vt.edu
Supervisor: Dr. Helen Crawford, 231-6520
Chair, Human Subjects Committee, Dr. Dave Harrison, 231-6581
Chair, Institutional Review Board, David Moore, 231-4991

SIGNATURE: _____

DATE: _____

PHONE: _____

Appendix B: Medical Screening Questionnaire

The following information is required by the Institutional Review Board to screen for possible participation in subsequent EEG studies. We must know if you have had any medical problems that might keep you from participating. It is important that you be as honest as you can. This is kept confidential.

Age _____ Sex: Male ___ Female ___

1. Since birth have you ever had any medical problems? Yes No If yes, please explain.

2. Since birth have you ever been hospitalized? Yes No If yes, please explain.

3. Have you ever hit your head and experienced a concussion? Yes No If yes, please explain.

4. Did you ever have problems where you saw a counselor, psychologist or psychiatrist? Yes No If yes, please explain.

5. Do you use tobacco (smoke, chew)? Yes No If yes, please explain.

6. Have you had any hearing problems? Yes No If yes, please explain.

7. What is your current weight and height?

8. Do you currently have or have you ever had any of the following? Circle yes or no.

Yes No strong reaction to cold weather

Yes No circulation problems

Yes No tissue disease

Yes No skin disorders (other than facial acne)\

Yes No arthritis

Yes No asthma

Yes No lung problems

Yes No heart problems/disease

Yes No diabetes

Yes No hypoglycemia

Yes No hypertension

Yes No low blood pressure

Yes No high blood pressure

Yes No hepatitis

Yes No neurological problems

Yes No epilepsy or seizures

Yes No brain disorder

Yes No stroke

If you have circled yes to any of the above conditions, please explain.

9. Have you ever been diagnosed formally to have had:

Yes No learning deficiency or disorder

Yes No reading deficiency or disorder

Yes No attention deficit disorder

Yes No attention deficit hyperactivity disorder

10. Do you have

Yes No claustrophobia (high fear of smaller closed rooms)

Yes No high fear of needles or blood

11. List any over-the counter prescription medications you are presently taking:

12. Do you have or have you ever had any other medical conditions that you can think of? If yes, please note them below.

Appendix C: Tobacco Use Questionnaire

Tobacco Use (Modified Fagerström): Version 2 (August 1999)

Below are some questions about your use of tobacco. Please answer every statement, even if you are not completely sure of the answer. Read every statement carefully, but do not spend too much time deciding on the answer.

How old are you? _____ Sex: Male _____ Female _____

ETHNICITY Which do you consider yourself to be (circle all that apply)

1. African-American 2. Asian 3. Hispanic 4. White, non-Hispanic
5. American Indian 6. Asian Pacific Islander 7. Other

_____

1. Have you ever smoked tobacco cigarettes? No __ Yes __
   smoked cigars? No __ Yes __
   smoked pipe? No __ Yes __
   chewed tobacco? No __ Yes __

If you have ever smoked or chewed tobacco, please continue. If not, go to next questionnaire

2. Presently do you smoke tobacco cigarettes? No __ Yes __ If yes, Everyday? No ___ Yes ___
   smoke cigars? No __ Yes __ If yes, Everyday? No ___ Yes ___
   smoke pipe? No __ Yes __ If yes, Everyday? No ___ Yes ___
   chewed tobacco? No __ Yes __ If yes, Everyday? No ___ Yes ___

3. At what age did you begin smoking cigarettes? ____ years old
   smoking cigars? ____ years old
   smoking pipes? ____ years old
   chewing tobacco? ____ years old

4. We are interested in knowing how many years you have used tobacco, and for how long you ever quit doing it:

# of years you have smoked tobacco ____ years from 19__ to 19__, 19__ to 19__, 19__ to 19__, 19__ to 19__

How many times, and for how long did you quit smoking? (Be as precise as possible)

0 times __ 1 time __ 2-5 times __ more than 5 times __

Length of time during which you did not smoke (note each time)

# of years you have chewed tobacco ____ years from 19__ to 19__, 19__ to 19__, 19__ to 19__, 19__ to 19__

How many times, and for how long did you quit chewing? (Be as precise as possible)

0 times __ 1 time __ 2-5 times __ more than 5 times __

Length of time during which you did not chew (note each time)

5. Presently, on the average, how many cigarettes/cigars per day do you smoke?

0 __ 1 or 2 __ 3 – 10 __ 11-19 __ 20-30 (pack or more) __ 31 or more __

6. Presently, if you chew, on the average, how many chews per day do you have?

0 __ 1 or 2 __ 3 – 10 __ 11-19 __ 20-30 (pack or more) __ 31 or more __

7. In the past, what was the most tobacco per day that you used on a regular basis?

Cigarettes: _____ Cigars: _____ Pipes: _____ Chews: _____

8. When do you use tobacco more frequently?

More during the first hours after waking than during rest of day? ___ yes ___ no
More during the middle of the day than early morning or at night? ___ yes ___ no

More during the evening hours than during rest of day? ___ yes ___ no

About the same throughout the day ___ yes ___ no

9. We often get something positive from using tobacco. What does it do for you? Explain fully.

10. Are there any negative things you get from smoking? Yes ___ No ___ If yes, explain:

11. Which time of the day would you hate most to give up your tobacco, and why?

12. If you have to go without tobacco in the morning hours, does this affect you in any way? Yes __ No __

If yes, explain.

13. How do you feel and what do you do if you are on a plane (train, bus) and cannot smoke?

14. How soon after you wake up do you usually have your first smoke? _____ minutes

15. How soon after you wake up do you usually have your first chew? _____ minutes

16. Do you wake up at night to smoke? Yes ___ No ___ Average # of nights per week _____

17. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in cinema, etc.)

___ yes ___ no

18. Do you smoke when you are so ill that you are in bed most of the day?

___ yes ___ no

19. When you first started smoking/chewing, how quickly did you get hooked in it (that is, found it hard to quit)? Explain fully.

20. After you first started smoking/chewing, how long did it take you to increase to a constant level? Explain fully.

Appendix D: Alcohol Use Questionnaire

This information will be used confidentially with only your subject number. We wish to determine if you drink alcohol or not, as it might affect your EEG.

1. **Since January of this year,** on the average how many drinks do you have when you drink alcohol? (one drink equals 12 oz beer, 4 oz wine, or 1 - 1 1/2 oz of hard liquor)

__ 1. I did not drink alcohol during this time period
__ 2. 1-2 drinks
__ 3. 3-4 drinks
__ 4. 5-6 drinks
__ 5. 7-8 drinks
__ 6. 9-12 drinks
__ 7. 13-16 drinks
__ 8. 17 or more

2. **OVER THE PAST TWO WEEKS,** on the average how many drinks per day do you have when you drink alcohol?
(one drink equals 12 oz beer, 4 oz wine, or 1 - 1 1/2 oz of hard liquor)

__ 1. I did not drink alcohol during this time period
__ 2. 1-2 drinks
__ 3. 3-4 drinks
__ 4. 5-6 drinks
__ 5. 7-8 drinks
__ 6. 9-12 drinks
__ 7. 13-16 drinks
__ 8. 17 or more

3. On how many occasions **OVER THE LAST TWO WEEKS** did you consume five or more drinks at one sitting?
(one drink = 12 oz beer, 4 oz wine; 1 - 1 1/2 oz of hard liquor)

__ 1. I did not drink alcohol during this time period
__ 2. 1-2 occasions
__ 3. 3-4 occasions
__ 4. 5-6 occasions
__ 5. 7-8 occasions
__ 6. 9-12 occasions
__ 7. 13-16 occasions
__ 8. 17 or more
__ 9. I drank alcohol, but always less than five drinks at one sitting

4. When was the last time you drank alcohol and how much did you drink?

Appendix E: Drug Usage Questionnaire

Please use the following scale to indicate, on the average, how often you have used each of the following drugs **IN THE LAST MONTH.**

1. Never
2. Once a month or less
3. Couple of times a month
4. Once a week
5. Several times a week
6. Daily

1. ___ Alcohol (beer, wine, liquor) last time (date): _____
2. ___ Coffee last time (date): _____
3. ___ Herbal Ecstasy last time (date): _____
4. ___ Pills for Staying Alert While Studying (e.g., Vivarin)
   last time (date): _____
5. ___ Inhalants (such as nitrous oxide) last time (date): _____
6. ___ Steroids last time (date): _____
7. ___ Pain Relievers last time (date): _____
8. ___ Prescription Amphetamine (e.g. diet pills) last time (date): _____
9. ___ Prescription Ritalin/other drugs for ADD last time (date): _____
10. ___ Prescription Sedatives, Tranquilizers, Antidepressants
    last time (date): _____
11. ___ Other uppers or downs _____ last time (date): _____
12. ___ Marijuana (pot, hash, hash oil) last time (date): _____

If you have used any of the following drugs in the last 4 weeks, we would appreciate your terminating the study. The reason we need to do this is to make sure that any effects on EEG is due to the tobacco and not an interaction with another unknown

substance. You will still be paid for your participation. We will not ask you why so that we can keep confidentiality.

Ecstasy (MDMA, but not herbal ecstasy)	psychedelic drugs (LSD, PCP, mushrooms)
Amphetamine (speed)	Ketamine (Special K, animal tranquilizer)
Cocaine (crack, etc)	Opiates (heroin, smack, horse)

Appendix F: Family History

We are assessing for sensory gating for tones … that is, how much your brain responds to two tones close to one another. Typically, an individual shows a reduction to the second tone because of habituation (getting used to it). In the literature, individuals with certain psychiatric disorders (and also their close relatives) may show a deficit in sensory gating. For this reason, we would like to know if any of your first degree family members have been diagnosed with a psychiatric disorder. You will participate in the experiment regardless of your family history, but we need to know this to better understand your responses. This sheet will be kept from your data files.

I am adopted and I do not know _____

I am not adopted _____

Mother (blood relative) _____

Father (blood relative) _____

Siblings (blood relative) _____

_____

_____

_____

_____

_____

_____

_____

Your Children (blood relative) _____

_____

Appendix G: Experiment Stimuli Experience Questions

FIRST STIMULI

Were the standard and unusual tones the same loudness or different? _____

If different, which was louder? _____

Were you able to predict when the flash was going to happen? _____

If so, how? _____

For the pairs of tones:

How many pairs were there? _____

Was the first louder, the second louder, or were they the same? _____

For the pairs of clicks:

How many pairs were there? _____

SECOND STIMULI

Were the standard and unusual tones the same loudness or different? _____

If different, which was louder? _____

Were you able to predict when the flash was going to happen? _____

If so, how? _____

For the pairs of tones:

How many pairs were there? _____

Was the first louder, the second louder, or were they the same? _____

For the pairs of clicks:

How many pairs were there? _____

Figure 1. Paired-pulse evoked potentials showing P50 suppression in smokers and never-smokers (Crawford et al., 2002).

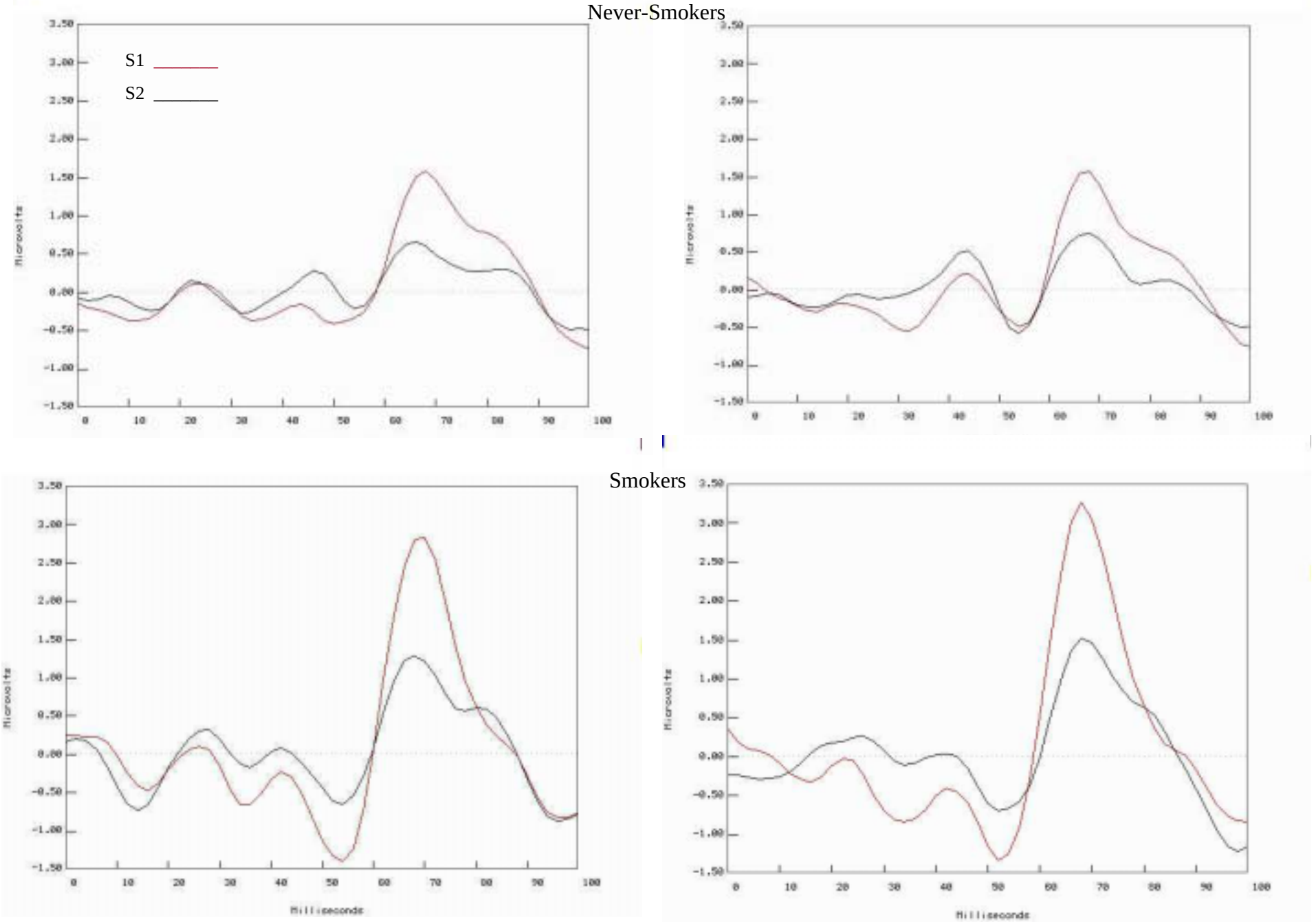


Figure 2. Example of oscillatory EEG activity.

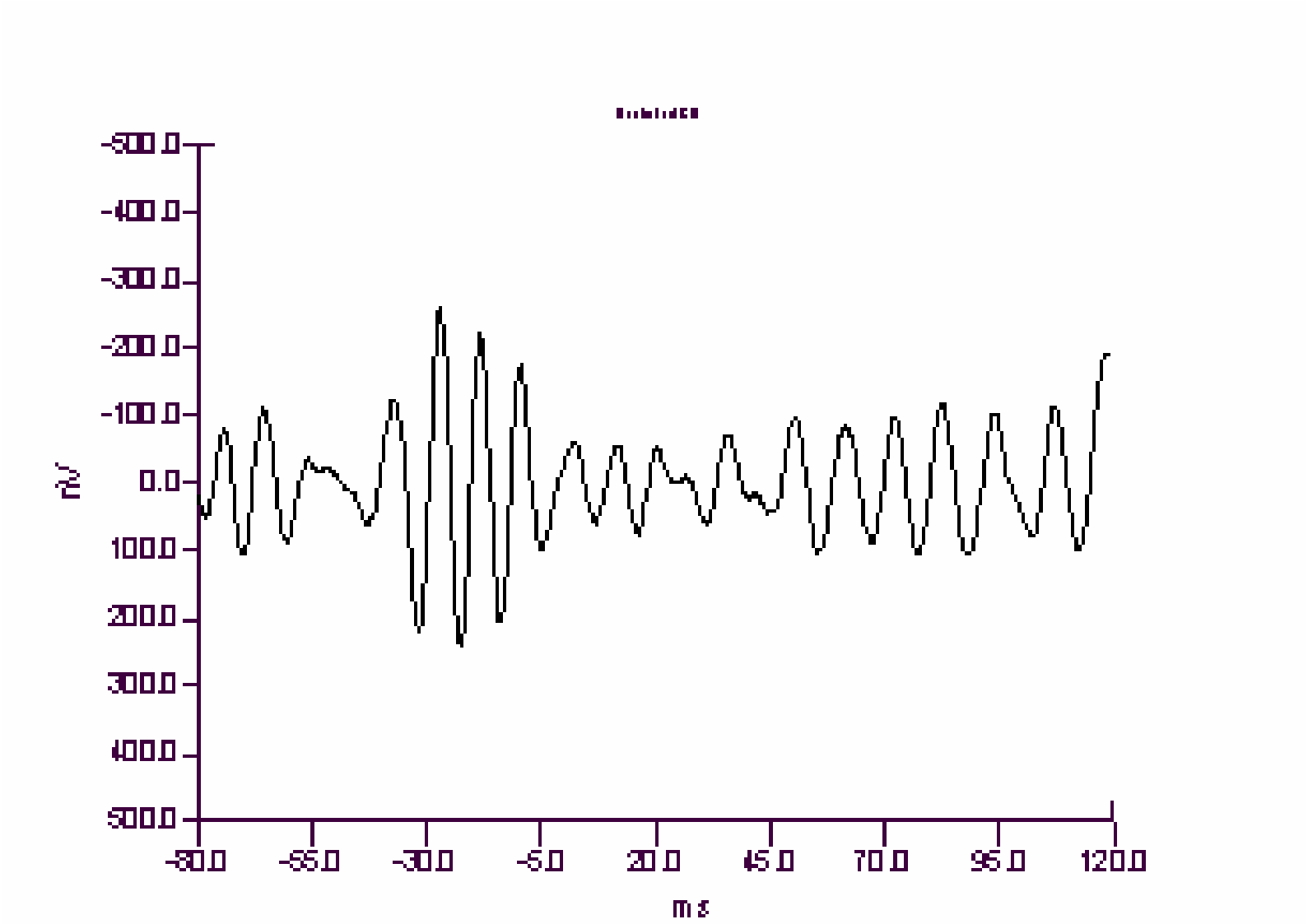


Figure 3. Evoked transient 40 Hz response an MAVA transform.

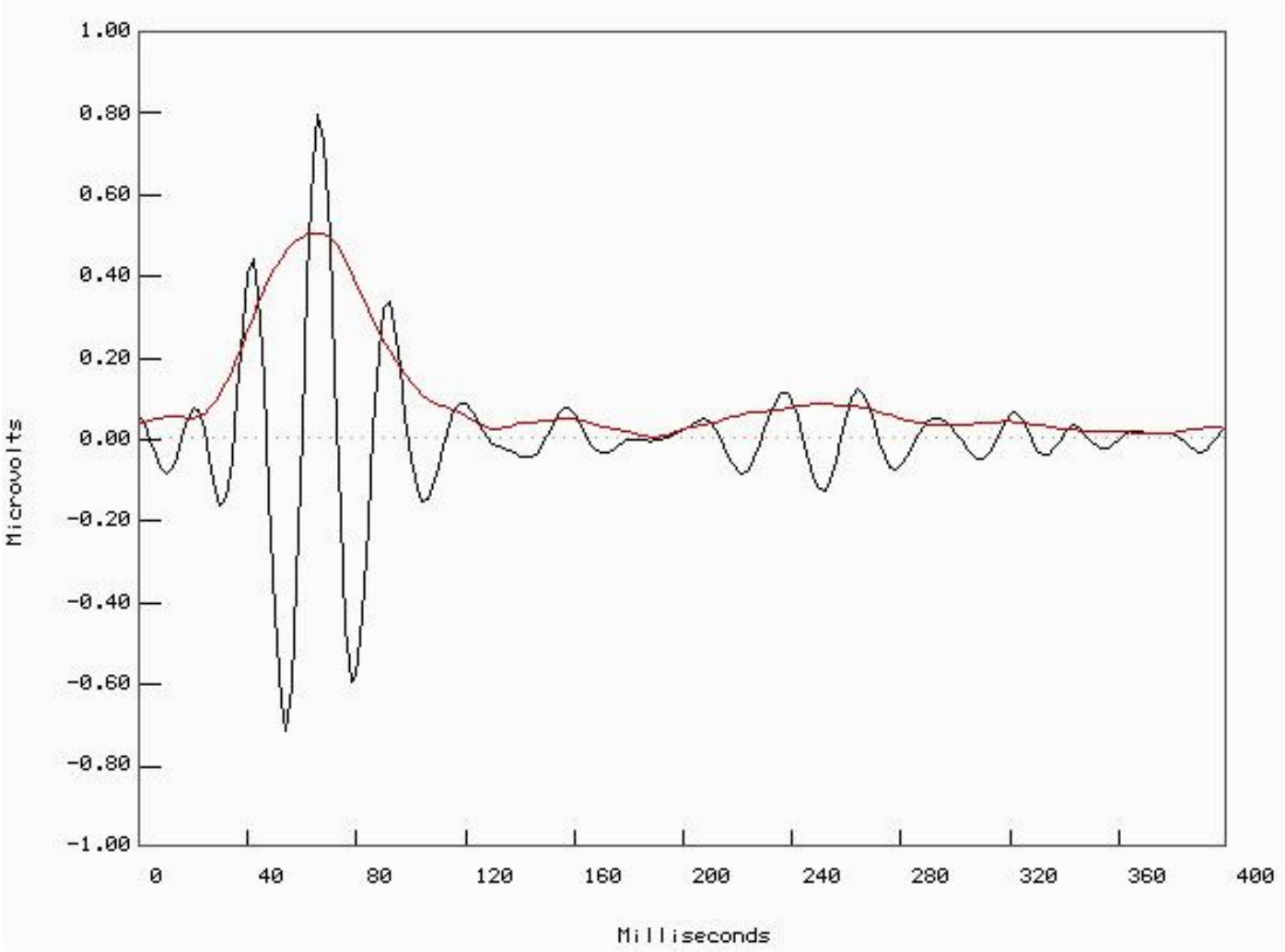


Figure 4. Transient 40 Hz MAVA data baseline through 120 msec.

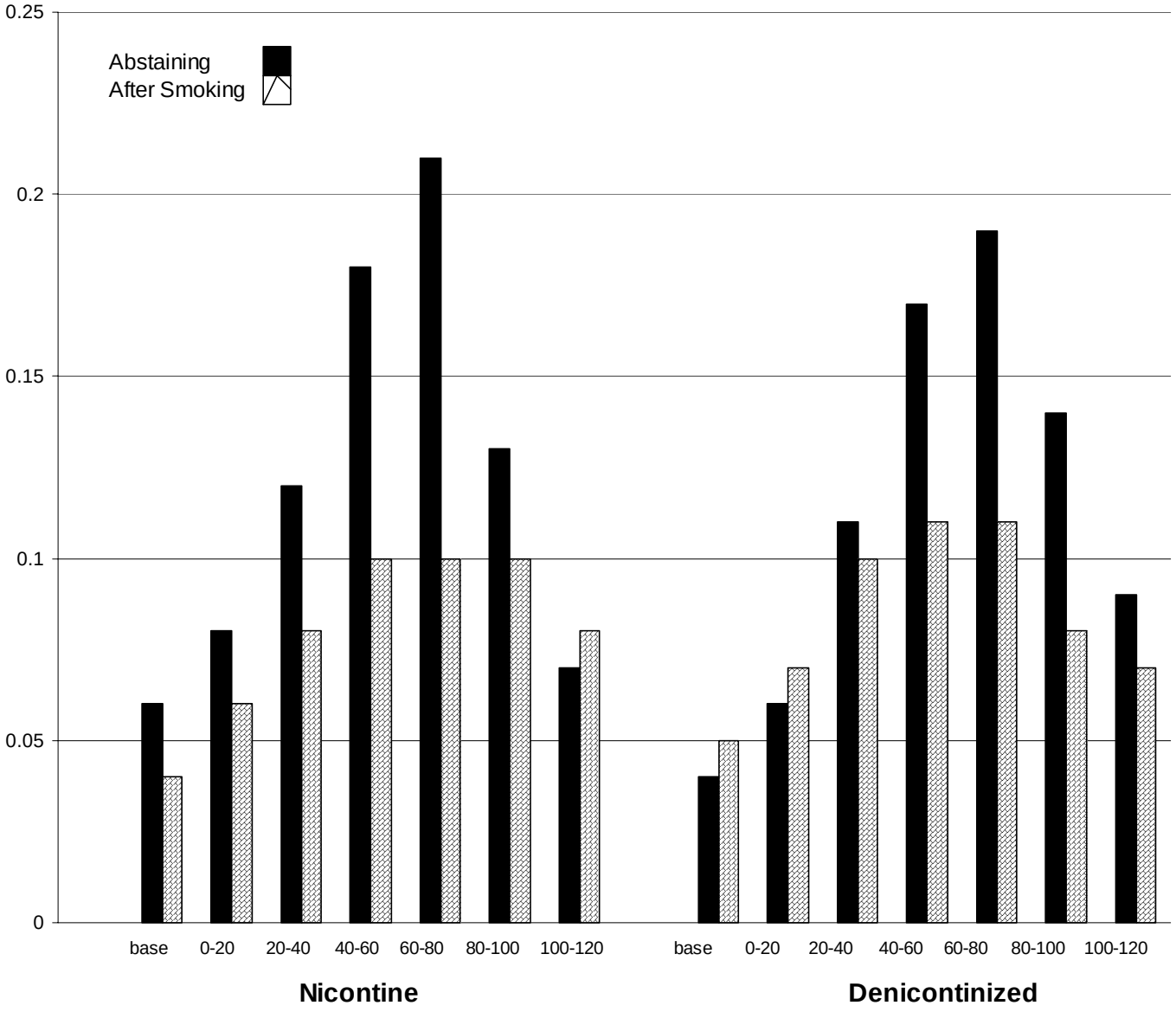


Figure 5. Transient 40 Hz MAVA data baseline through 120 msec smokers vs. never-smokers (McClain-Furmanski et al., in preparation).

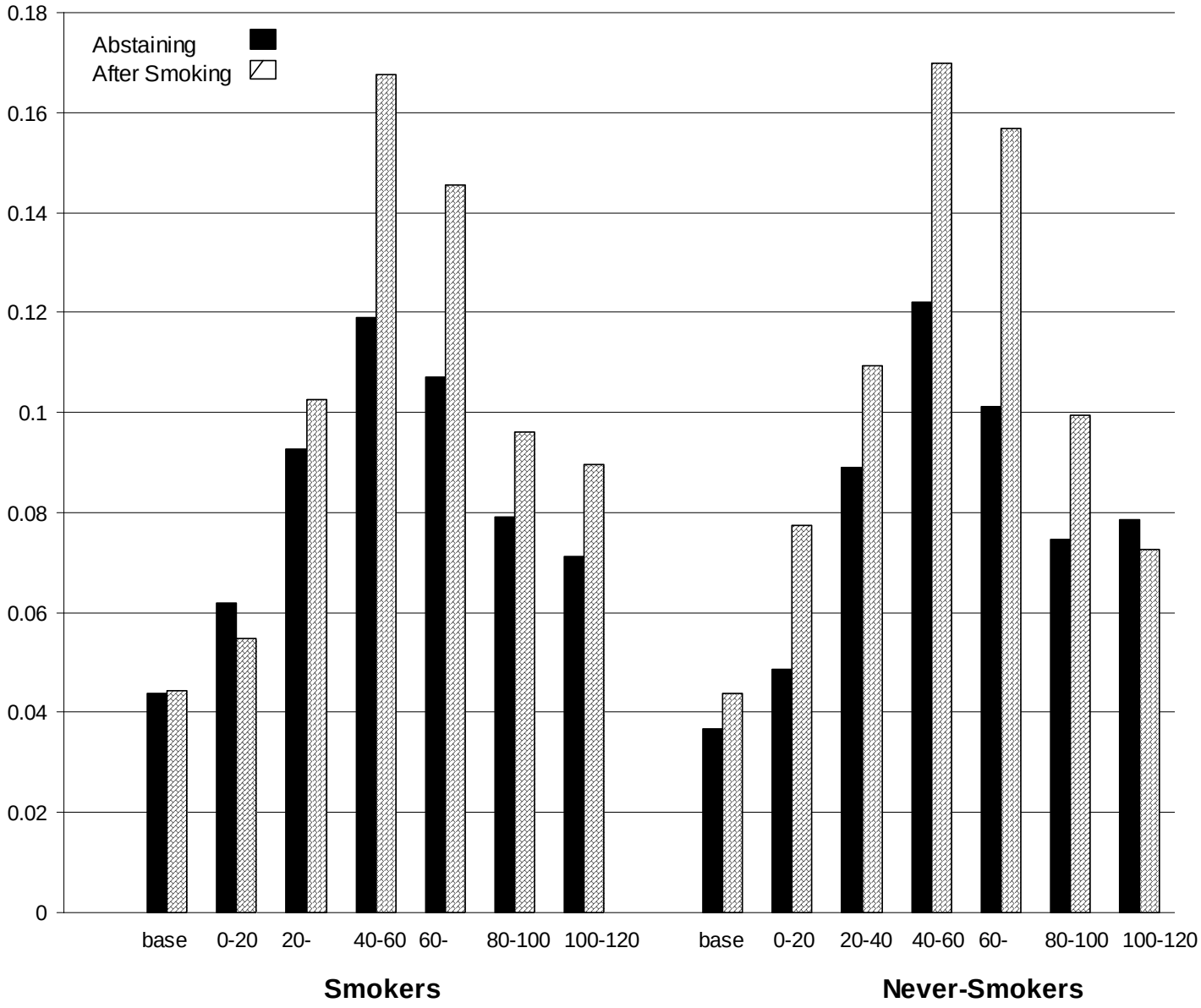
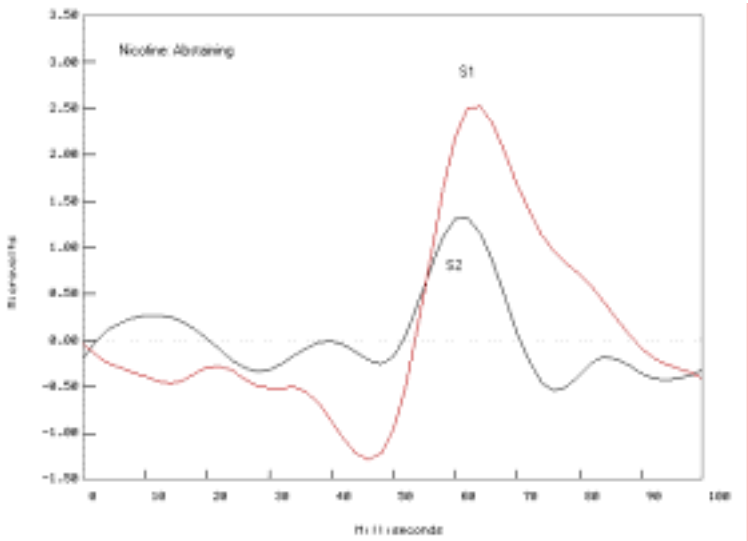
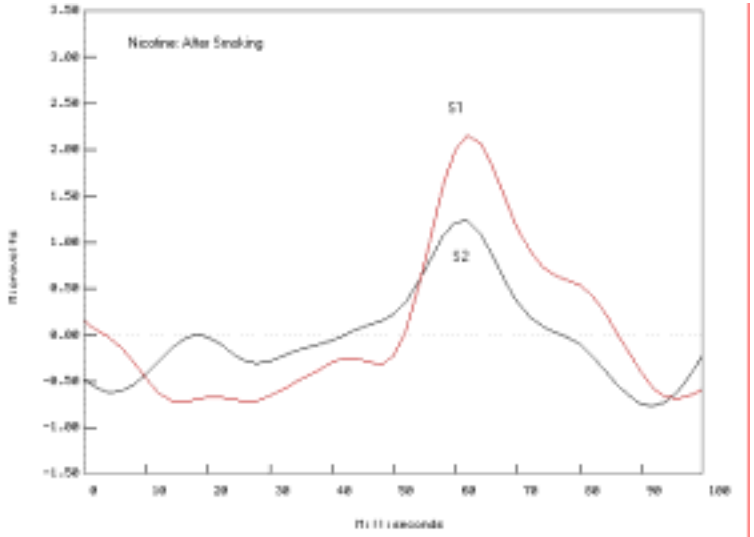


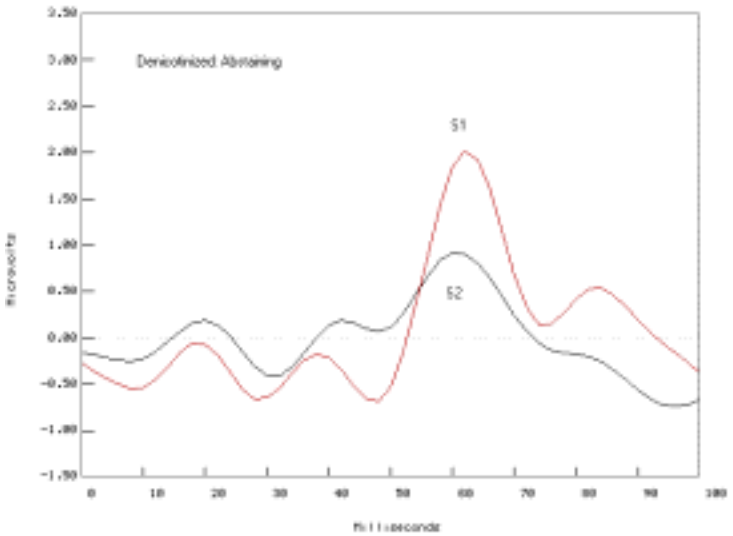
Figure 6. Paired-pulse evoked potentials showing P50 suppression in nicotine vs. denicotinized groups.

Nicotine





Denicotinized



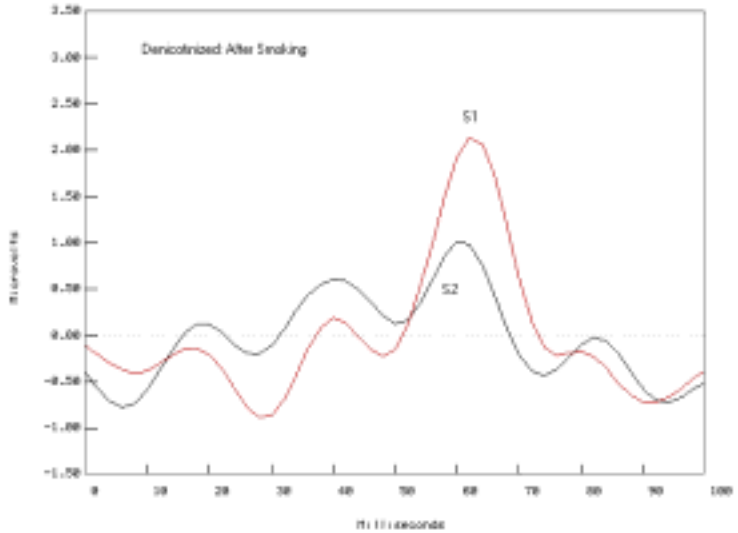
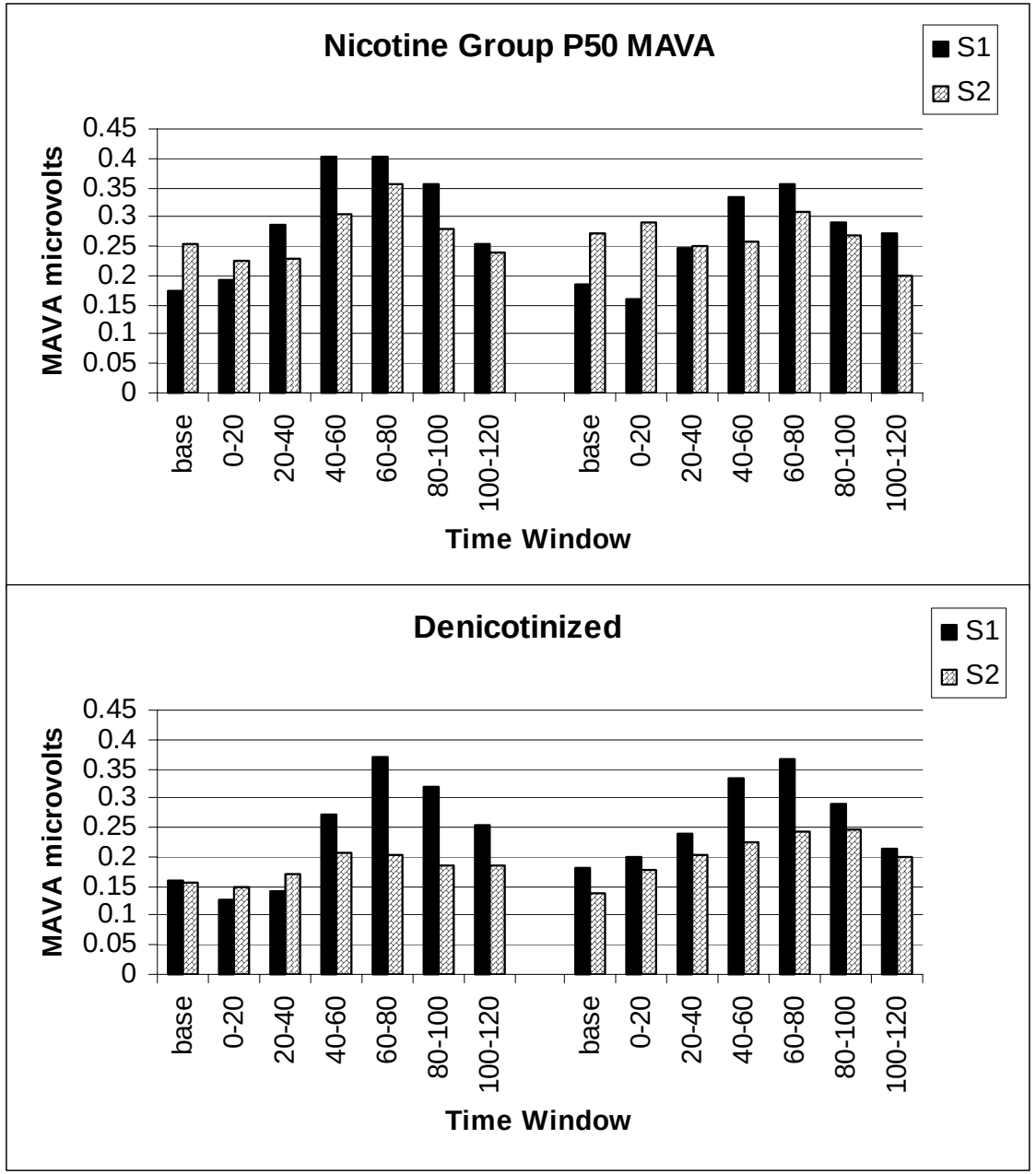


Figure 7. Paired-pulse MAVA data baseline through 120 msec in nicotine vs. denicotinized groups.



Abstaining

After Smoking

Figure 8. Paired-pulse MAVA data baseline through 160 msec in never-smokers vs. smokers after smoking (Crawford et al., 2002).

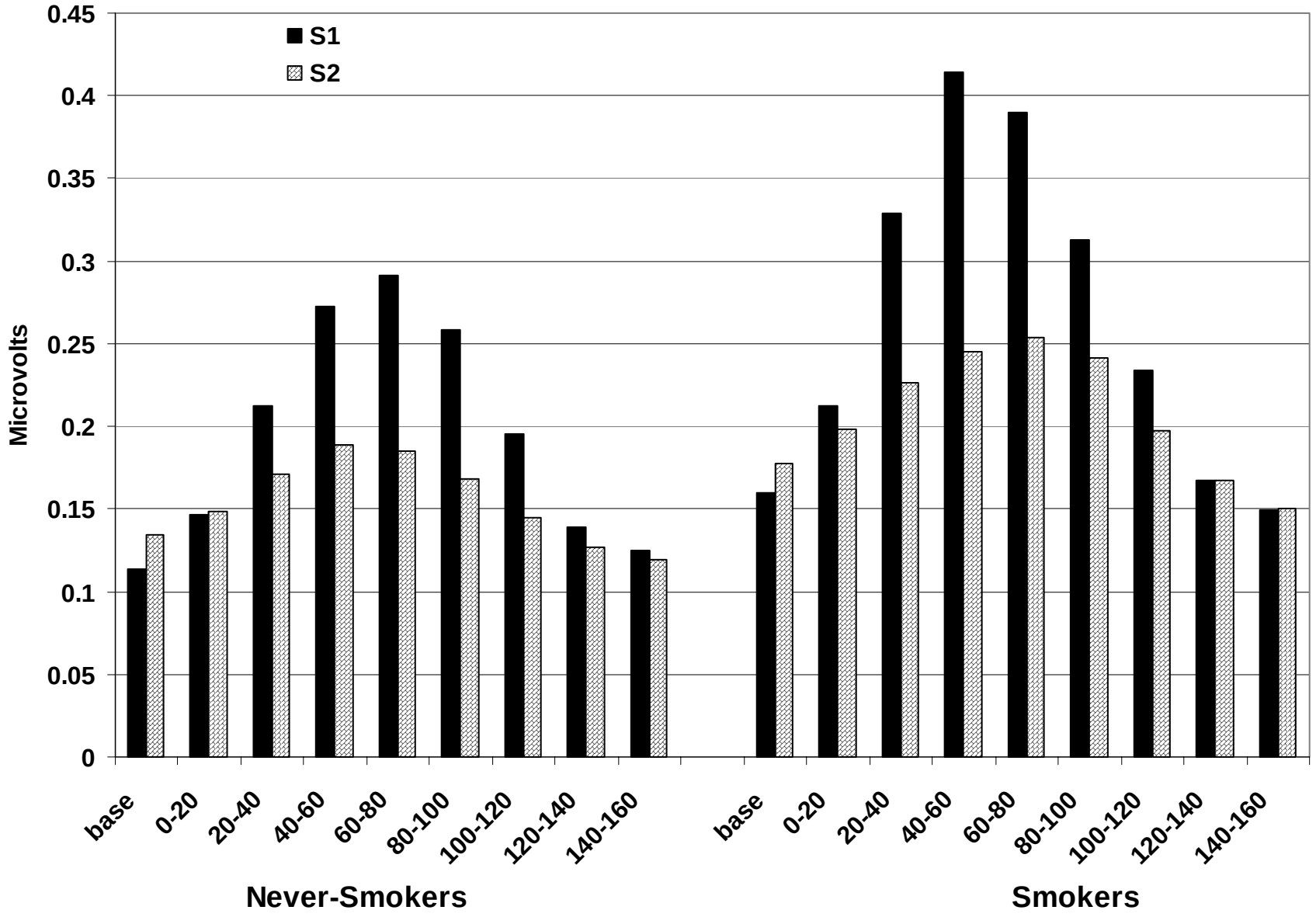
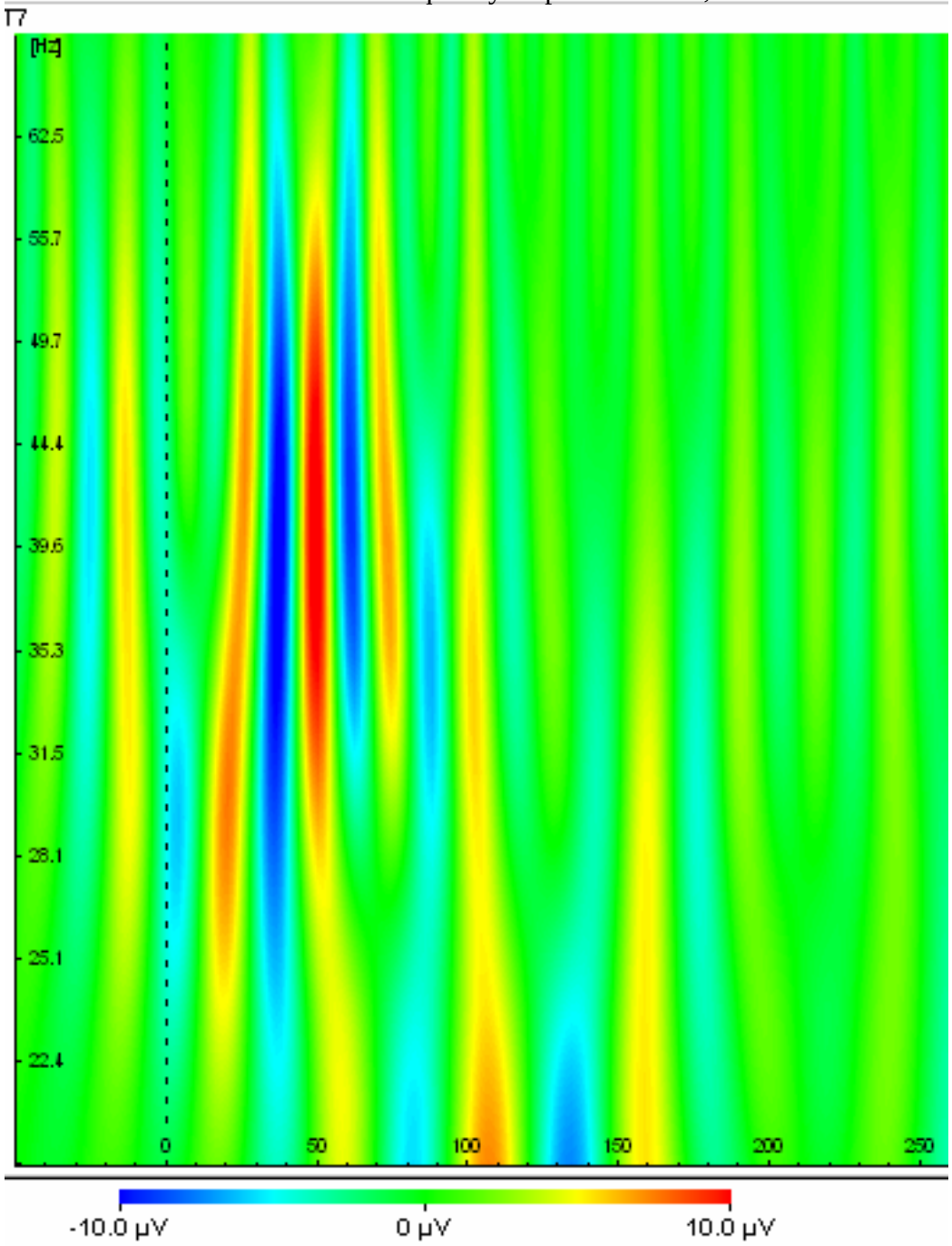


Figure 9. Continuous wavelet transform time frequency map 20 to 70 Hz, -50 to 250 msec.



Curriculum Vitae

Dennis McClain-Furmanski

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Home phone: (540) 381-8538
Email: dmcclain@vt.edu

EDUCATION

Present:

Doctoral candidate in Experimental Psychology, Psychological Sciences Area, Department of Psychology, Virginia Polytechnic Institute and State University, Blacksburg, VA. Sucessfully completed training and prelims. Supervisor, Helen Crawford.

Dissertation in progress: Synchronized Gamma Oscillations Underlying Mid-latency Auditory Evoked Potentials: Assessment of Effects of Psychopharmacologically Active Components of Tobacco.

Prior:

MA Psychology (Experimental Focus), Radford University, Radford, VA, Dec. 1997 Supervisor: Karl Pribram, BRAINS Center. Thesis: EEG Power Ratios During Cognitive Load in ADHD and Normal Adults.

MS Community Health Education (Health Care Management Focus), Old Dominion University, Norfolk, VA, August 1996. Supervisor, Colin Box, College of Health Sciences. Thesis: Telemedicine: Discovering and Overcoming the Barriers.

BS Psychology (Clinical Focus, including practicum) Old Dominion University, Norfolk, VA, May 1994, Summa Cum Laude.

Additional Educational Experience and Professional Training:

Santa Fe Institute for Complex Systems Studies. Attended Complex Systems Summer School, June 1999, under NSF full tuition and support scholarship grant.

Human Brain Mapping: Workshop on Methodological Issues and State of the Art. International Conference on Human Brain Mapping. June 1998, Montreal, Quebec.

Virginia Substance Abuse Counselor training, Old Dominion University, Continuing Education Dept. Training includes 1 year clinical practicum.

Professional Licensure

Certified Substance Abuse Counselor, Dept. Of Health Professions, Commonwealth of Virginia, license # 0710-000-996, current through June. 2003. 3.5 years experience in clinical setting at Serenity Lodge, Chesapeake, VA.

Professional Affiliations

Cognitive Neuroscience Society, student member.

The Organization for Human Brain Mapping, student member.

Society for Neuroscience, student member.

Healthcare Information and Management Systems Society, student member.

Teaching Experience

Lab instructor for: Undergraduate Methods and Statistics (2 semesters); Motivation (1 semester); Cognitive Psychology (1 semester); Sensation and Perception (3 semesters); Psychophysiology (3 semesters).

Recitation instructor: Introductory Psychology (3 semesters).

Primary instructor: Developmental Psychology (1 semester), Cognitive Psychology (1 semester), Sensation and Perception (1 semester).

Lab Manager: Physiological Psychology Lab, Virginia Tech (6 semesters).

PUBLICATIONS

Crawford, H.J., Horton, J.E., McClain-Furmanski, D., & Vendemia, J. (1998). Brain Dynamic Shifts During The Elimination Of Perceived Pain And Distress: Neuroimaging Studies of Hypnotic Analgesia. On-line Proceedings of the 5th Internet World Congress on Biomedical Sciences '98 at McMaster University, Canada (available from URL: http://www.mcmaster.ca/inabis98/simantov/dus0133/index.html).

McClain-Furmanski, D., Castagnoli, N., Castagnoli, K., & Crawford, H. J. (2000) Prepulse Inhibition: Differences in Smokers and Never-smokers. Neuroimage, 11, S-48.

Crawford, H.J., McClain-Furmanski, D., Castagnoli, N., & Castagnoli, K. (2002) Enhancement of auditory sensory gating and stimulus-bound gamma band (40-Hz) Oscillations in Heavy Tobacco Smokers. Neuroscience Letters, 317, 151-5.

PAPERS UNDER PREPARATION:

Crawford, H. J., McClain-Furmanski, D., & Horton, J. E., . Inhibition of pain: Somatosensory event-related potentials changes during hypnotic analgesia in high but not low hypnotizable individuals.

Crawford, H. J., McClain-Furmanski, D., & Horton, J. E., . Underlying gamma oscillations (40 Hz) during pain and hypnotic analgesia: Evidence for pre-attentive processing differences in low and highly hypnotizable individuals.

McClain-Furmanski, D., Crawford, H. J. & Alho, K. Mismatch Negativity in Healthy Smokers: Evidence of Effects of Tobacco on Perceptual Acuity.

McClain-Furmanski, D., Crawford, H.J., Castagnoli, N., & Castagnoli, K. Time Series Analysis of Transient 40 Hz Gamma Band Oscillations in Tobacco Users.

REFEREED ABSTRACTS:

Crawford, H. J., Horton, J. E., Hirsch, T. B., Harrington, G. S., Plantec, M. B., Vendemia, J. M. C., Shamro, C., McClain-Furmanski, D., & Downs III, J. H. (1998) Attention and Disattention (Hypnotic Analgesia) to Painful Somatosensory TENS Stimuli Differentially Affects Brain Dynamics: A Functional Magnetic Resonance Imaging Study. International Journal of Psychophysiology, 30(1-2), 77.

Horton, J. E., McClain-Furmanski, D., Mészáros, I., & Crawford, H. J. (1998) To Inhibit Pain is to Actively Shift Conscious Awareness: Somatosensory Event-Related Potential Evidence During Hypnotic Analgesia. International Journal of Psychophysiology, 30(1-2), 234-235.

Crawford, H. J., Horton, J. E., Hirsch, T. B., Harrington, G. S., McClain-Furmanki, D., & Downs III, J. H. (November 1998) Brain Dynamics of Hypnotic Analgesia: New Evidence from SERP and functional Magnetic Resonance Imaging Studies. International Journal of Clinical and Experimental Hypnosis.

REFEREED SCIENTIFIC PRESENTATIONS:

Richardson, E., Concannon, M., Daroy, M., Harrington, J., Hope, K., Pappert, C., Petrazzuolo, E., Randle, T., Raybuck, S., Thomas, R., Vraneza, M., Walls, M., Williams, A. & McClain-Furmanski, D. (October, 2001). Effects of Room Lighting on Reaction Time and Heart Rate in Adults With and Without ADD. Poster presented at Society for Psychophysiological Research, Montreal, QE.

McClain-Furmanski, D., Castagnoli, N., Castagnoli, K., & Crawford, H. J. (August, 2000). Effects of tobacco on sensory gating mechanisms ("P50"). Poster presented at the American Psychological Association annual meeting, Washington, D.C.

McClain-Furmanski, D., Castagnoli, N., Castagnoli, K., & Crawford, H. J. (June, 2000) Prepulse Inhibition: Differences in Smokers and Never-smokers. Poster presented at Human Brain Mapping Conference, San Antonio TX.

McClain-Furmanski, D., Horton, J. E., & Crawford, H. J. (April, 1999). Inhibition of pain: Effects on Somatosensory event-related potentials during hypnotic analgesia in high but not low hypnotizable persons. Presented at Cognitive Neuroscience Society meeting, Washington, D.C.

Crawford, H. J., Horton, J. E., Hirsch, T. B., Harrington, G. S., McClain-Furmanki, D., Downs III, J. H. Brain Dynamics of Hypnotic Analgesia: New Evidence from SERP and functional Magnetic Resonance Imaging Studies. International Journal of Clinical and Experimental Hypnosis, November 1998.

Crawford, H. J. Horton, J., Hirsch, T. B., Harrington, G. S., Plantec, M. B., Vendemia, J. M. C., Shamro, C., McClain-Furmanski, D., and Downs III, J. H. (October 1998). Attention and Disattention (Hypnotic Analgesia) to Painful Somatosensory TENS Stimuli Differentially Affects Brain Dynamics: A Functional Magnetic Resonance Imaging Study. Invited Paper for Symposium on "New Perspectives on Brain Imaging of Human Pain and Pain Control: Symposium in Remembrance of Bonica" (Chair: Andrew Chen). 9th World Congress of Psychophysiology, Sicily, Italy.

Horton, J. E., McClain-Furmanski, D., Mészáros, I., & Crawford, H. J. (September, 1998). To inhibit pain is to actively shift conscious awareness: Somatosensory event-related potential evidence during hypnotic analgesia. Paper presented at 9th World Congress of Psychophysiology, Sicily, Italy.

McClain-Furmanski, D., Diaz, D., Shan, P. J., King, J., Pierce, Y., & Pribram, K. (October 1996). Dynamical spectral analysis of running EEG in Attention Deficit and Control subjects. Poster presented at the Conference on Behavioral Neurodynamics, Radford University

McClain-Furmanski, D. (April 1994). Computerized metacommunication: The communication necessary to operate a communication network. Paper Presented at Southeastern States Communications Society Conference, Undergraduate Honors Presentations.

McClain-Furmanski, D. Human Overload: Cultural Adjustment to Overpopulation. Paper presented at Undergraduate Anthropology Conference, Wright State University, Ohio, Mar 1983.

Conferences

Society for Psychophysiological Research, October, 2001, Montreal, QE.

International Conference on Human Brain Mapping. June 2000, San Antonio, Texas.

American Psychological Association, April 2000, Washington DC

First Conference of Brain and Communication: Conscious and Unconscious Processing. April1999, Georgetown University.

Cognitive Neuroscience Society Annual Conference, April 1999, Washington DC.

Second Radford BioFusion Research and Development Discussion Group. Sponsored in part by NASA-Langley Research Center and Martin-Marietta, July 1999.

International Conference on Human Brain Mapping. June 1998, Montreal, Quebec.

Conference on Behavioral Neurodynamics III (1994), IV (1995), and V (1996), Radford University, Radford, VA

Southeastern States Communications Society Conference, April 1994, Norfolk, VA.

Scientific and Technical Expertise

Computer Operations

Operating Systems: Windows/MS-DOS, MacOS, Unix (System V Unix, Silicon Graphics IRIX, Red Hat Linux, Slackware Linux, muLinux).

Stimulus Control: Neuroscan STIM, and MS-DOS batch file programming with direct control of serial interface.

Data Acquisition: Neuroscan SCAN EEG workstation via SynAmps amplifiers; Electrical Geodesics 128 channel EEG bioamplifiers; Lexicor Neurosearch 24 channel EEG/electrophysiology workstation; Coulbourn general electrophysiological testing 8 channel bioamplifiers using DataQ acquisition software.

Data Analysis: Matlab (signal/time series analysis), SAS, SPSS, SYSTAT, LabStat, Excel, CODAS physiological data software for Coulbourn bioamps; SCAN, Electrical Geodesics and Lexicor EEG internal analysis programs (including programming of automated mass/batch data analyses).

Electronics and Computer Hardware: 30+ years experience as electronic/computer technician. Designed and constructed various computer interfaces and specialized devices for biofeedback, and perceptual stimulus presentation and testing.

Community Service and Other Activities

Producer and DJ, “Inside The Circle”, Native American music and news based radio show, WUVT-FM, 4 years. Professional member of the Native American Music Awards.

Student member of Virginia Tech YMCA, Native American Program

Student/alumni member Radford University Native American Heritage Association

Military Service

US Air Force, 1975 to 1979, fuel systems technician. Honorable discharge, Vietnam era service.

Indiana Army National Guard, 1985 to 1986, ambulance commander. Honorable discharge to active duty.

US Army, 1985 to 1989, fuel systems technician. Honorable discharge with service connected disability.