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ORIGINAL INVESTIGATION

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The P300 brain potential is reduced in smokers

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Abstract *Rationale:* Tobacco smoking is the most prevalent type of substance abuse, yet its biobehavioral etiology is little understood. Identification of differences between smokers and non-smokers on basic characteristics of neurocognitive functioning may help to elucidate the mechanisms of tobacco dependence. *Objectives:* This study assessed the relationship between smoking status and the P300 component of event-related potential (ERP) while controlling for potential confounders such as alcoholism, drug abuse, and psychopathology. *Methods:* The ERP responses elicited by a visual oddball task were measured at the mid-parietal site in 905 current smokers, 463 ex-smokers, and 979 never smokers. *Results:* P300 amplitude was significantly lower in current cigarette smokers compared to never-smokers. Ex-smokers did not differ significantly from never-smokers. P300 reduction was also associated with alcoholism, drug dependence, and family density of alcoholism. However, after controlling for smoking, only family density of alcoholism remained a significant predictor of P300 amplitude. *Conclusions:* The results indicate a significant effect of smoking status on P300 amplitude which is additive to family history of alcoholism and suggest that either (1) long-term tobacco smoking may produce a reversible change in brain function, or (2) reduced P300 may be a marker of risk for nicotine dependence.

Key words ERPs · P300 · Smoking · Nicotine · Addiction

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Introduction

Tobacco smoking is the most prevalent type of dependence and is associated with serious medical problems, yet basic neurobehavioral mechanisms of nicotine addiction are little understood. Previous studies (Ashton and Golding 1989; Gilbert 1995; Houlihan et al. 1996; Ilan and Polich 1996) involving electrophysiological techniques have primarily focused on acute effects of smoking and suggested that nicotine may facilitate cognitive performance and improve mood, through the relief of withdrawal-related decrements as well as through direct stimulant effects. However, whether smokers differ from non-smokers on some baseline measures of neurocognitive functioning that might be associated with vulnerability to addiction has not been well studied.

Research suggests a strong association between smoking and alcohol dependence, which in part might be explained by common genetic liability (Heath and Madden 1995; Swan et al. 1996). Alcohol and nicotine dependence may be mediated by some common neurobiological pathways (Nevo and Hamon 1995; Nisell et al. 1995; Fowler et al 1996). Previous studies have shown that a substantial proportion of alcoholics and individuals at risk for alcoholism exhibit a reduced P300 component of the brain event-related potential (ERP) (Porjesz et al. 1998). Within families of alcoholics, the reduction is greatest in affected individuals, in agreement with the presumed increased genetic liability (Porjesz et al. 1998), although task and population variables contribute to this effect (Polich et al. 1994). The suggestion that diminished P300 may reflect a genetic variation of brain

function is further supported by the evidence for substantial heritability of P300 amplitude in the general population (Eischen and Polich 1994; van Beijsterveldt and Boomsma 1994; Katsanis et al. 1997). Given the potential overlap between genetic vulnerabilities for smoking and drinking, it is reasonable to ask whether regular smokers also show a reduced P300 amplitude.

The goal of this study was to examine the P300 amplitude in regular cigarette smokers, ex-smokers, and never-smokers (individuals who never smoked on a regular basis). The sample was drawn from families participating in the Collaborative Study on the Genetics of Alcoholism (COGA). COGA included families selected for high density of alcoholism and control families, which offered an opportunity to delineate the relationships and possible interactions between P300, smoking status, alcoholism, and family density of alcoholism. The following issues were addressed: 1) is P300 amplitude reduced in cigarette smokers, and 2) is the relationship to smoking independent of the relationship to alcoholism and/or family density of alcoholism?

Material and methods

Subjects

Subjects were drawn from two types of families participating in the Collaborative Study on the Genetics of Alcoholism (COGA): 1) densely alcoholic families (at least three alcohol dependent individuals per family) which were ascertained through an alcoholic proband, and 2) control families randomly ascertained from sources such as driver license records (low density of alcoholism). The study was approved by the appropriate Review Board for human research. Informed consent was obtained from all participants. Assessment of smoking and alcoholism were based on the semi-structured psychiatric interview designed for use in genetic studies of alcoholism (SSAGA) (Bucholz et al. 1994). The diagnosis of alcoholism was based on the DSMIIIR criteria for alcohol dependence. "Smoking" was defined as daily cigarette smoking for a month or more. Drug dependence was defined as the presence of one or more DSMIIIR diagnoses of dependence on specific drugs. Data used in this study (n=2347, 1325 females) originate from six participating COGA laboratories. Separate analyses of data from individual laboratories produced the same pattern of findings as reported below, with the exception of one laboratory, where a non-significant trend in the same direction was observed. Subjects were within the age range of 17–74 years (mean 37; SD=13). Alcohol dependence was diagnosed in 957 participants; of 1390 non-alcoholics, 849 (high family density group, HFD) originated from families with high density of alcoholism, and 541 (low family density group, LFD) were from control families. The sample included 905 current daily cigarette smokers (mean±SD: 20±10 cigarettes daily) 979 never-smokers (subjects who never smoked on a daily basis for a month or more) and 463 ex-smokers (19±15 cigarettes daily) who quit smoking 1 year or more prior to examination. Subjects who quit less than 1 year prior to testing (n=54) were not included in the analysis, nor were subjects practicing other forms of tobacco use (pipes, cigars, chewing, snuff). Actual numbers may vary slightly for individual analyses due to missing data on smoking or ERP variables.

No formal instructions were given to subjects regarding abstinence from smoking prior to the ERP testing. They abstained, however, for about 1 h during preparation for testing. Alcoholic subjects were required to have abstained from alcohol for at least 5 days and non-alcoholics for 24 h prior to ERP assessment. A breath analysis test was performed to confirm the absence of alcohol.

ERP recording and analysis

ERPs were recorded from 19 scalp electrodes referred to the nose, with two electrodes placed at the outer canthus of the left eye and on the forehead to monitor eye movements. Trials with EEG and electrooculogram signals exceeding ±73.3 μV were rejected automatically. Subjects sat in a dimly lit, sound-attenuated, electrically shielded room. ERPs were elicited by stimuli presented on a computer monitor (1 m away) for a duration of 60 ms with interstimulus intervals of 1.6 s. The target stimulus was a white "X" (4 cm^2, or 2.9°; novel stimuli (5 cm^2, or 3.6°) were non-repeating colored geometric shapes arranged in variegated patterns, and the standard stimulus was a white square (4 cm^2, or 2.9°). The target and novel stimuli each occurred with a probability of 0.125, and the standard stimulus occurred with a probability of 0.75. Subjects were instructed to focus on a fixation point located in the center of the monitor, to press a keypad with their forefinger whenever a target stimulus was detected, and to refrain from responding when the novel or standard stimuli occurred. Response speed was emphasized, but not at the cost of accuracy, and response hand was counterbalanced across subjects. Stimulus presentation was concluded when 25 target, 25 novel, and 150 standard artifact-free (i.e., no signal >73 μV) ERP trials were acquired. Time-on-task ranged from 7 to 10 min. Signals were amplified with a bandpass of 0.02–50 Hz (3 dB down, 6 dB per octave slope) and digitized at a rate of 256 Hz. Averaged waveforms were low-pass filtered digitally with cutoff at 32 Hz prior to component identification and measurement. ERP analysis for each of the three types of stimuli consisted of locating the most positive component in the latency window from 275 to 575 ms. Amplitude was measured relative to the mean of the 187 ms prestimulus baseline, with peak latency defined as the time point of maximum positive amplitude within the latency window. Only the P300 component elicited by target stimuli at the midline parietal (Pz) electrode was analyzed for the present report. At this location, P300 is maximum, and its measurement is optimal under these conditions (Porjesz et al. 1998). Amplitude values lower than –20 μV relative to the baseline were considered outliers and excluded from analysis. Trials with incorrect subject's response to target stimuli (signal misses) were also excluded.

Age and gender correction

A preliminary analysis demonstrated that females produced greater P300 amplitudes than males [$F(1,1273)=16.1$; $P<0.0001$]. Also, P300 amplitude was inversely correlated with age (r=–0.40; $P<0.001$). Hence, each gender group was subjected separately to an age correction of the P300 amplitude values using linear regression. The resulting standardized residuals were then used as gender- and age-adjusted P300 amplitude scores. Statistical distribution of this variable did not depart from normality (Kolmogorov-Smirnov test was non-significant). The original P300 amplitude data were also used in general linear models (GLM) procedure with age as a covariate and gender as a cofactor to delineate individual effects of smoking status, alcoholism, and family density of alcoholism on P300 amplitude and to test for their interaction. In addition, psychopathology diagnoses (lifetime major depression and antisocial personality disorder; use of medication, and amount of drinking) were included in GLM analyses to test for possible confounding of the smoking-P300 association. Type III sum of squares was used for partitioning of variance in an unbalanced design, and the effect of each variable was evaluated after all other factors had been accounted for.

Results

Figure 1 illustrates group-averaged ERP waveforms for groups differing in smoking status. P300 amplitude was significantly different among current smokers, ex-smok-

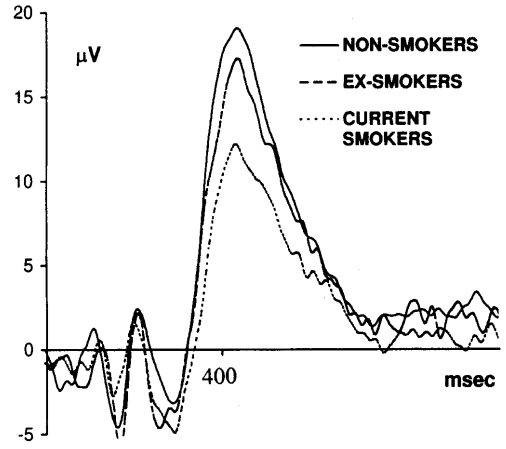

Fig. 1 Grand average ERP waveforms elicited by the visual target stimulus at the mid-parietal (*Pz*) location. These waveforms are based on a portion of the data from the Missouri COGA laboratory (71 never-smokers, 35 current smokers, and 27 ex-smokers) and are representative of data obtained from all contributing laboratories

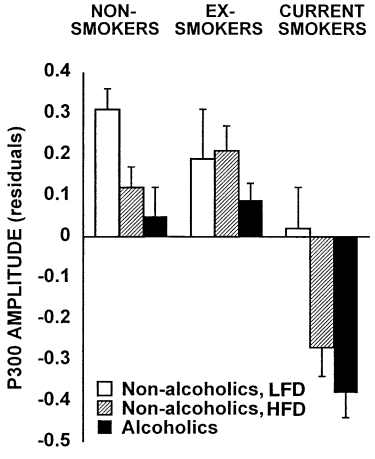

Fig. 2 Mean (±SE) age- and gender-corrected target P300 amplitude (standardized residuals) in current smokers, ex-smokers, and never-smokers. The results are presented separately for individuals from families with high (*HFD*) and low (*LFD*) density of alcoholism and for alcoholics from HFD families

ers, and never-smokers [14.8, 16.5, and 19.3 μV, respectively; one-factor ANOVA for uncorrected amplitude values: $F(2,2346)=65.6$, $P<0.0001$].

Figure 2 presents the mean age- and gender-corrected peak amplitude values. ANOVA performed using age- and gender-corrected values (standardized residuals) also indicated significant group differences [$F(2,2346)=70.7$, $P<0.0001$].

Pairwise group comparisons using *t*-test with Bonferroni correction of *P*-values demonstrated a significant reduction of P300 amplitude in current smokers compared to never-smokers ($P<0.0001$). Ex-smokers did not differ significantly from never-smokers ($P>0.5$), whereas the difference between ex-smokers and current smokers was significant ($P<0.001$). Inspection of statistical distributions indicated that these group differences represent a

Table 1 Prevalence of smoking and alcoholism in the studied sample. *HFD* families with high density of alcoholism, *LFD* control (low density) families. All alcoholics were from HFD families

	Never-smokers	Current smokers	Ex-smokers
Alcoholics	176	577	204
Non-alcoholics, HFD	426	259	164
Non-alcoholics, LFD	377	69	95

systematic trend, rather than effect of outliers. A test for homogeneity of variance did not reveal any significant heterogeneity among groups (Levene's statistic: 0.846, $P>0.4$). The mean values and standard deviations for the raw (uncorrected) P300 amplitudes were 19.5±8.9 μV for never-smokers, 15.0±8.4 μV for current smokers, and 16.6±8.3 μV for ex-smokers (it should be noted that these group means may depend on age and gender distribution in different groups). Reaction time of the subjects' responses to target stimuli (assessed on a part of COGA data) was not significantly related to either P300 amplitude or smoking.

The amount of daily cigarette consumption showed only a non-significant trend toward inverse relationship with P300 amplitude ($P>0.3$). In ex-smokers, the recency of smoking cessation was not significantly related with P300 amplitude.

To elucidate the contribution of alcohol dependence and family density of alcoholism (HFD versus LFD) to these results, the effect of these factors on P300 amplitude as well as their possible interaction with smoking were examined. Since pairwise tests did not show a significant difference between never-smokers and ex-smokers, further analyses were focused on never-smokers and current smokers. The breakdown of the sample by smoking status and alcoholism is shown in Table 1.

Alcohol dependence was significantly associated with smoking status ($\chi^2=229.0$, $df=2$, $P<0.001$) with 60.3% of alcoholics being current smokers versus 30.5% of non-alcoholics from the HFD families. In LFD families, only 12.8% of non-alcoholics were current smokers. There association between smoking status and family type was significant ($\chi^2=66.4$, $df=2$, $P<0.001$).

Consistent with previous studies (Porjesz et al. 1998), a one-way ANOVA showed significant main effects of alcoholism [$F(1,1886)=24.8$; $P<0.0001$] and FDA [$F(1,1425)=17.9$; $P<0.0001$] on P300 amplitude. Separate and combined effects of smoking, alcoholism, and FDA on P300 amplitude (dependent variable) were further examined using general linear models (GLM) procedure with age as a covariate and gender as a co-factor. The effect of each factor was evaluated after all other factors have been accounted for. The effect of alcoholism was non-significant after adjusting for current smoking and FDA [$F(1,1958)=0.3$, $P>0.5$]. In contrast, the effect of current smoking remained significant [$F(1,1958)=14.4$, $P<0.001$] when controlled for alcoholism and FDA, suggesting that the main effect of alcohol-

ism is largely confounded by its high association with smoking status. No significant interaction between alcoholism and smoking status was observed. The effect of smoking was larger than the effect of alcoholism: on average, current smokers differed from never-smokers by 0.5 SD, which corresponds to an absolute P300 amplitude difference of 4–5 μV. Alcoholics differed from non-alcoholics by about 0.2 SD (absolute amplitude difference of about 2 μV). Current smoking was associated with a higher level of alcohol consumption (number of drinks in a typical week) both in alcoholics and non-alcoholics ($P<0.001$); however, controlling for the amount of drinking did not diminish the effect of smoking. It is important to note that P300 amplitude reduction observed in subjects from densely alcoholic families (HFD) compared to LFD remained significant after controlling for both smoking and alcoholism [$F(1,1958)=17.2$, $P<0.001$].

A parallel analysis of the effects of drug dependence (one or more DSMIIIR diagnoses of drug dependence endorsed) showed that it was associated with decreased P300 amplitude [$F(1,1048)=13.4$; $P<0.001$], although this effect was no longer significant after correcting for smoking status ($P>0.2$). Even after adjusting for both alcoholism and drug dependence, the effect of smoking on P300 amplitude remained highly significant [$F(1,821)=46.3$; $P<0.0001$]. None of the potential confounders tested (psychopathology, drinking, use of medication) appeared to be accountable for the P300-smoking association.

Discussion

The results indicate that current smokers produce lower visual P300 amplitudes than never-smokers. The effect of smoking history was independent of and greater than the effects of alcoholism, alcohol consumption, and drug dependence. Given the high prevalence of smoking in alcoholics compared to the general population, the present findings suggest that smoking may contribute substantially to the P300 amplitude differences between alcoholics and non-alcoholics observed in previous studies (Porjesz et al. 1998). It is important to note that the effect of family density of alcoholism (FDA) on the P300 amplitude documented in previous studies (Pfefferbaum et al. 1984; Polich et al. 1994; Porjesz et al. 1998) remained highly significant after controlling for smoking. Smoking and FDA appear to diminish P300 amplitude in an additive fashion.

Decreased P300 has also been associated in previous studies with other forms of psychopathology, including antisocial personality disorder, conduct disorder, attention deficit disorder, dementia, schizophrenia and depression, and substance dependence (Pfefferbaum et al. 1984; Carlson et al., 1999). Given the increased prevalence of tobacco smoking in these conditions (Glassman 1993; de Leon 1996), the present findings imply that ERP differences between disease groups and controls could be confounded by differential prevalence of smoking in a manner similar to a variety of biological variables (e.g., gender, handedness, recency of food intake, etc.) known to affect P300 measures (Polich and Kok 1995). The results of the present study thus strongly suggest that smoking has to be included as an important covariate in ERP studies involving between-subjects designs, in particular, in studies of alcoholism and psychopathology.

Several interpretations of the relationship between P300 and smoking can be offered. One possibility is that P300 reduction in regular smokers may be partly explained by the effects of nicotine withdrawal. However, there is no consistent evidence that P300 amplitude is reduced by minimal smoking deprivation (Houlihan et al. 1996; Ilan and Polich 1996). Moreover, participants in this study were not required to abstain from smoking for a lengthy period before the ERP tests.

Another plausible interpretation of these findings is that P300 amplitude reduction may be a consequence of chronic tobacco smoking, which may lead to neurochemical changes or impairments of neurocognitive functioning. This interpretation is supported by neuroimaging studies indicating a decreased cerebral blood flow in smokers, which may improve following the cessation of smoking (Meyer et al. 1995; Rourke et al. 1997).

Yet another possible interpretation is that low P300s may be associated with a greater vulnerability to nicotine addiction, stronger dependence, and reduced ability to quit once an individual has started smoking on a regular basis. Accordingly, low P300 found in current smokers may be a marker of risk for developing nicotine dependence. In contrast, ex-smokers would be expected to show higher P300 (similar to never-smokers) in accord with the presumed smaller liability. Hence, P300 reduction may be associated with smoking persistence (i.e., probability of not quitting successfully once regular smoking has been initiated) rather than with smoking initiation itself. Heath et al. (1995) and True et al. (1997) have presented evidence suggesting that smoking persistence might have a stronger and more direct genetic basis than does the initiation of smoking. This genetic risk factor may overlap with that associated with alcoholism (Swan et al. 1996; consistent with evidence that P300 is reduced both in alcoholics and their children, even before the onset of regular drinking (Porjesz et al. 1998).

The association between smoking, alcoholism, and P300 is consistent with an interpretation of P300 amplitude reduction as constituting a more general factor of risk for different forms of addictive behaviors that may result from common neurotransmission-related deficits. Like other substances of abuse, nicotine activates the mesolimbic dopamine system, and this effect appears to be essential for the reinforcing properties of nicotine (Ashton and Golding 1989; Nisell et al. 1995). Vulnerability to both smoking and alcoholism may be mediated by common alterations of brain neurotransmission systems that influence P300 amplitude, a conclusion supported by evidence that dopamine is involved in the neu-

rophysiological mechanisms which generate and/or modulate P300 (Stanzione et al. 1991; Hansenne et al. 1995).

In conclusion, P300 ERP amplitude is reduced in current tobacco smokers, but ex-smokers do not differ significantly from never-smokers. However, as yet it is unclear whether reduced P300 amplitude is a consequence of smoking or a pre-existing condition. Because P300 is influenced by genetic factors, the amplitude decrement may be a marker of a broader vulnerability to addiction and associated psychiatric diseases. Further studies must clarify the nature of P300 reduction in smokers and its implications for neuropsychiatric research.

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