Frontal P300 Decrements, Alcohol Dependence, and Antisocial Personality Disorder

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Background: *The purpose of this study was to examine the independent and interactive effects of alcohol dependence, antisocial personality disorder (ASPD), and age on brain function.*

Methods: *P300 event-related potentials (ERPs) were recorded from 393 alcohol-dependent and 170 non–alcohol-dependent adults while they performed a visual oddball task. The two subject groups were further subdivided based upon age and the presence/absence of ASPD.*

Results: *Alcohol dependence was associated with a significant P300 amplitude decrement at anterior electrode sites only. Antisocial personality disorder was also associated with reduced P300 amplitudes at anterior electrode sites; however, the effects were only significant among subjects 30 years of age or younger. To validate this association between ASPD and P300 amplitude a correlational analysis was performed; the correlation between anterior P300 amplitude and the total number of childhood conduct disorder and adult ASPD symptoms was significant.*

Conclusions: *The P300 amplitude decrement found at anterior electrode sites among subjects with ASPD is consistent with the results of numerous ERP, neuroimaging, or neuropsychologic studies of anterior brain function. Our study is unique in suggesting that the effects of ASPD on anterior brain function are best detected during early adulthood. The study also suggests that the detrimental neurophysiologic effects of alcohol dependence predominantly involve the anterior brain.* Biol Psychiatry 2000;47:1064–1071 © *2000 Society of Biological Psychiatry*

Key Words: P300, evoked potentials, alcohol dependence, antisocial personality disorder, conduct disorder, EEG

Introduction

The functional integrity of the central nervous system in patients afflicted with chronic alcohol dependence has long been of interest. During the 1970s, a number of neuropsychologic studies demonstrating impaired executive functioning and cognitive inflexibility led to a theory of frontolimbic brain pathology in chronic alcoholism (Tarter 1973; Tarter and Parsons 1971). More recent studies have continued to support this hypothesis (Chmielewski and Golden 1980; Ciesielski et al 1995; Pishkin et al 1985).

In addition to the neuropsychologic studies, neuroimaging studies employing positron emission tomography (PET) or single photon emission computed tomography (SPECT) have implicated frontal brain dysfunction as a reliable correlate of chronic alcoholism. Positron emission tomography and SPECT findings have included demonstrations of diffuse hypometabolism in the frontal lobes (Sachs et al 1987; Volkow et al 1992, 1994; Wang et al 1992) as well as more focused deficits in the anterior cingulate (O'Carroll et al 1991) and other anterior regions of the frontal lobes (Nicolas et al 1993). Several investigators have detected significant correlations between frontal hypometabolism in alcohol-dependent patients and performance deficits on neuropsychologic tasks related to frontal lobe functions (Adams et al 1993; Dao-Castellana et al 1998; Gilman et al 1990; Samson et al 1986). The frontal hypometabolism found in alcoholic patients could be the result of a functional deficit and/or a loss of neurons within the superior frontal cortex or frontal cingulate gyri (Cala 1987; Kril and Harper 1989; Pfefferbaum et al 1997).

A number of researchers have demonstrated abnormalities in the resting electroencephalogram (Bauer 1997; Costa and Bauer 1997; for a review see Bauer, in press) and in various types of evoked electroencephalographic potentials (for a review see Porjesz and Begleiter 1996) in chronic alcoholics. Most relevant to the hypothesis of frontolimbic dysfunction is a study by Biggins and colleagues (1995) demonstrating prolonged latency of a subcomponent of the P300 (viz., P3a) event-related poten-

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tial (ERP) among elderly chronic alcoholics. The neuronal generator of this subcomponent is believed to reside within the frontal brain (Knight 1984).

Unfortunately, in many neuropsychologic and neuroimaging studies of alcohol-dependent patients, the complicating or confounding effects of comorbid psychiatric or medical conditions are rarely considered. Antisocial personality disorder (ASPD) is one psychiatric disorder that has been demonstrated to have a high comorbidity with alcohol dependence in both clinical and community samples (cf. Helzer and Pryzbeck 1998; Hesselbrock and Hesselbrock 1997; Hesselbrock et al 1985). Furthermore, several lines of evidence, deriving from neuropsychologic, cerebral metabolic, and ERP studies (Bauer et al 1994a, 1994b; Dao-Castellana et al 1998; Kuruoglu et al 1996; Raine et al 1994), suggest that ASPD itself is associated with deficits in frontal brain functioning (for a review see Giancola 1995).

For example, authors of neuropsychologic studies of children with conduct disorder (the childhood precursor of ASPD) or other behavioral disorders have consistently found deficits in both verbal and executive cognitive functioning (Giancola et al 1998; for reviews see Giancola, in press; Moffitt 1993), though some of these studies did not control for the effects of substance abuse. Frontal lobe dysfunction, estimated by neuropsychologic test performance, is also commonly reported in antisocial adults (Deckel et al 1996; Gillen and Hesselbrock 1992; Lapierre et al 1995; for a review see Kandel and Freed 1989).

In an interesting study that examined the effects of both alcohol dependence and ASPD, Kuruoglu and colleagues (1996) utilized SPECT to show that alcoholics with a comorbid diagnosis of ASPD exhibited regional cerebral blood flow reductions within the frontal lobes. These frontal cerebral blood flow reductions were not found in alcoholic patients or in nonalcoholic volunteers without ASPD. In another study, PET technology was used to demonstrate reduced regional glucose metabolism in the prefrontal cortex (i.e., orbitofrontal, anterior medial, superior frontal), but not in other brain regions, among violent criminals compared with age- and sex-matched control subjects (Raine et al 1994). The results of a similar study by the same investigators (Raine et al 1998) suggest that childhood psychosocial deprivation (e.g., neglect or abuse) is not a contributing factor to these prefrontal deficits.

Antisocial behavior has been associated with P300 amplitude reductions in alcohol/drug-dependent patients (Bauer 1997; Branchey et al 1988, 1993) as well as in individuals who are at risk for developing alcohol or drug dependence (Bauer and Hesselbrock 1999a, 1999b; Bauer et al 1994a, 1994b; O'Connor et al 1994). Branchey and colleagues found a significant negative correlation between P300 amplitude and self-reported aggression in alcoholics (Branchey et al 1988) and impulsivity in drug abusers (Branchey et al 1993). In another P300 study, Bauer (1997) detected a decrease in P3a amplitude in cocaine-dependent patients with ASPD, but not in a group of cocaine-dependent patients without ASPD. The P3a amplitude reduction was significantly correlated with the number of childhood conduct disorder symptoms.

In non–drug-dependent subjects, an association between reduced P300 amplitude and antisocial behavior has been found in children with conduct problems and in adults with ASPD (Bauer and Hesselbrock 1999a, 1999b; Bauer et al 1994a, 1994b; O'Connor et al 1994); however, several P300 studies of incarcerated criminals, with unspecified alcohol/drug use histories, have generated a contradictory result, with either null findings or a paradoxical enhancement of P300 amplitudes (Jutai et al 1987; Raine and Venables 1987, 1988). Two studies demonstrating a paradoxical enhancement of P300 in incarcerated criminals have been severely criticized on the basis of their ERP measurement techniques and their speculative interpretations of the results (cf. Howard 1989; Jutai 1989).

Several additional variables must be considered when examining the relationship between alcohol or drug use, personality traits, and neurophysiologic or neuropsychologic measures of brain function. For example, many studies have demonstrated that normal aging (i.e., brain maturation) is associated with a reduction in P300 amplitude (Brown et al 1983; Goodin et al 1978; Marsh 1975; Snyder and Hillyard 1977). Brain maturation can also interact with other variables, such as alcohol dependence or personality, and indirectly affect P300 amplitude.

We designed our study to examine the independent and interactive effects of alcohol dependence, ASPD, and age on visual P300 amplitude. It was hypothesized that alcohol-dependent subjects and subjects with ASPD would exhibit reduced frontal P300 amplitudes compared with their respective control subjects. In addition, it was hypothesized that alcohol-dependent individuals with ASPD would have more pronounced frontal P300 decrements compared with individuals with either alcohol dependence or ASPD. Age was expected to interact with both alcohol dependence and ASPD. More specifically, it was predicted that the detrimental effects of alcohol dependence on P300 amplitude would be greater in older subjects, reflecting the accumulated neurotoxic effects of alcohol. A strong hypothesis associating age and ASPD could not be justified from the extant studies of adults; however, because of our recent demonstration (Bauer and Hesselbrock 1999a) that age and conduct problems interactively affect P300 in adolescents, a similar interaction was expected in adults.

Methods and Materials

Subjects

Four hundred forty-four men and 119 women from the Collaborative Study on the Genetics of Alcoholism (COGA) project, 18–49 years of age, were included in the final analysis. These subjects were drawn from a larger ERP data set collected across six participating universities: Indiana University School of Medicine ($n = 67$); SUNY Health Science Center, Brooklyn ($n = 114$); University of California at San Diego ($n = 76$); University of Connecticut Health Center ($n = 130$); University of Iowa Health Center ($n = 55$); and Washington University School of Medicine ($n = 121$). Electroencephalography data were collected at each institution using identical experimental protocols, hardware, and software. A more detailed description of the larger study methodology can be found in Begleiter et al (1998) and Reich et al (1998). The larger COGA protocol included the recruitment of both affected families and control families; however, our study focused only on affected families in which the proband and two first-degree family members met criteria for alcohol dependence by both DSM-III-R and Feighner criteria.

Psychiatric diagnoses in all subjects were obtained via a highly reliable (Bucholz et al 1994) and valid (Hesselbrock et al 1999) polydiagnostic instrument, the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), designed for COGA. Individuals with serious psychiatric (i.e., mania, psychosis) or medical conditions (i.e., seizures, stroke, meningitis, heart or liver disease) were excluded from the analysis.

It was hypothesized that age would alter the effects of alcohol dependence and ASPD on P300. An examination of regression lines relating age to P300 were different in the four subject groups. Therefore, age could not be used as a covariate in a 2 by 2 factorial. Instead, the subject sample was split on the sample median age of 30 years (299 subjects aged 30 years or less vs. 264 subjects older than 30). Age was then included as an additional grouping factor. Eight subject groups were thereby created and contrasted in a $2 \times 2 \times 2$ factorial design: Alcohol Dependence (absent/present) $\times$ ASPD (absent/present) $\times$ Age ($\leq$30 vs. $>$30 years).The demographic and drug use characteristics of each group are presented in Table 1.

Procedure

Each subject was seated in a sound-attenuated chamber and was instructed to focus attention on a fixation point in the center of the screen. Each subject wore a fitted electrode cap (Electro-Cap International, Eaton, OH) containing the 21 leads in the montage of the International 10-20 System. The reference electrode was placed on the tip of the nose. A forehead electrode served as ground. Vertical and horizontal eye movements were monitored using electrodes situated about the eye. Artifact rejection (eye movement and EEG threshold = 73.3 μV p-p) was performed online. Electroencephalograph activity was amplified by a factor of 10 K (Sensorium EPA-2 Electrophysiology Amplifiers) and sampled at a rate of 256 Hz over a bandwidth of 0.02–50 Hz. Single-trial data, from −187 msec to +1313 msec relative to stimulus onset, were processed offline through a 32-Hz low-pass digital filter.

Table 1. Demographics and Drug Dependence

	Groups								
	Age ≤ 30				Age > 30				
Variables	1 (Alcohol Dependent)	2 (ASPD)	3 (Alcohol Dependent/ ASPD)	4 (control)	5 (Alcohol Dependent)	6 (ASPD)	7 (Alcohol Dependent /ASPD)	8 (control)	Statistic
Number	135	15	62	87	137	11	59	57	
% male	76	87	82	86	77	82	86	67	$\chi^2 = 12.3$
Years education	12.5 (2.0)	11.5 (2.1)	11.4 (1.7)	12.8 (1.9)	12.8 (2.0)	13.9 (2.6)	12.6 (2.2)	13.1 (1.7)	$F = 5.5^{a,b}$
Cocaine dependent (%)	34 (25)	3 (20)	36 (58)	7 (8)	47 (34)	3 (20)	35 (59)	2 (4)	$\chi^2 = 90.4^a$
Opiate dependent (%)	3 (2)	0	8 (13)	2 (2)	7 (5)	0	15 (25)	1 (2)	$\chi^2 = 50.7^a$
Stimulant dependent (%)	14 (10)	0	10 (16)	1 (1)	20 (15)	0	21 (36)	1 (2)	$\chi^2 = 52.6^a$
Sedative dependent (%)	6 (4)	0	8 (13)	0	9 (7)	0	18 (31)	0	$\chi^2 = 65.1^a$

ASPD, antisocial personality disorder.
[a] $p < 0.01$.
[b] 1, 4, 5, 6, 8 > 3; 6 > 2.

Three visual stimuli were presented—target (the letter *X*), frequent nontarget (square), and rare nontarget (colored geometric figures that changed on each trial)—with the following probabilities of occurrence: target (0.125), frequent nontarget (0.75), and rare nontarget (0.125). Each stimulus subtended a visual angle of 2.5°. Stimulus duration was 60 msec and the interstimulus interval was 1.6 sec. When the subject detected the stimulus, he or she responded with the right or left index finger and pressed a mouse button. The responding hand was randomized across subjects. Response speed was emphasized, but not at the cost of accuracy. The experiment terminated automatically after a minimum of 25 target, 150 frequent nontarget, and 25 rare nontarget artifact-free trials had been acquired. Trials with response times greater than 1000 msec were rejected.

For each subject, P300s elicited by target and rare nontarget stimuli were identified automatically. P300 was defined at each electrode as the highest positive peak within a time range of 275–575 msec after stimulus onset. P300 amplitude was measured as the voltage difference between the peak and the average voltage during the prestimulus period.

Table 2. Principal Components Factor Loadings for Target and Rare Nontarget Conditions

	Target components		Rare nontarget components	
Electrode	1	2	1	2
F3	.262	.920[a]	.937[a]	.179
F4	.284	.914[a]	.934[a]	.201
F7	.244	.823[a]	.816[a]	.177
F8	.212	.802[a]	.807[a]	.178
Fz	.269	.924[a]	.954[a]	.172
C3	.258	.400[a]	.815[a]	.493
C4	.397	.587[a]	.820[a]	.483
Cz	.553	.739[a]	.838[a]	.428
P3	.833[b]	.486	.503	.819[b]
P4	.834[b]	.479	.488	.819[b]
P7	.864[b]	.325	.252	.877[b]
P8	.871[b]	.296	.200	.889[b]
Pz	.774[b]	.539	.599	.716[b]
O1	.940[b]	.189	.110	.948[b]
O2	.938[b]	.183	.136	.940[b]

Rotation method: varimax with Kaiser normalization.
[a]Anterior component.
[b]Posterior component.

Results

Demographic Characteristics and Substance Use History

The demographic characteristics of the eight subject groups are presented in Table 1. Current and lifetime use of alcohol and other drugs, as well as DSM-III-R substance abuse and dependence, were assessed using the SSAGA. The prevalence rates of DSM-III-R cocaine, opiate, stimulant, and sedative dependence for each group are provided in Table 1.

Visual ERP Task: P300 Amplitude

To reduce the number of dependent variables and protect against type I error, principal components analyses were performed, separately, for the target and rare nontarget stimulus conditions. Two significant varimax-rotated factors (eigenvalue > 1.0), summarizing data from anterior (F3, F4, F7, F8, Fz, C3, C4, and Cz) and posterior (P3, P4, Pz, P7, P8, O1, and O2) electrode sites, were found for each condition. The posterior factor explained most of the P300 amplitude variance in the target stimulus ERP, and the anterior factor explained most of the variance in the rare nontarget stimulus ERP (Table 2). P300 amplitude was averaged across the electrodes within each factor, generating a mean P300 amplitude for the anterior and posterior regions. These summary scores were analyzed separately using $2 \times 2 \times 2$ (Alcohol Dependence $\times$ ASPD $\times$ Age) analyses of variance.

TARGET STIMULUS P300. A main effect of Age was found for both anterior [$F(1,109) = 4.72$, $p < 0.05$] and posterior P300 amplitude [$F(1,583) = 14.54$, $p < 0.001$]. In both anterior and posterior regions, younger subjects had greater P300 amplitudes: (anterior: $M_y = 11.1$ vs. $M_o = 9.0$ μV, posterior: $M_y = 13.1$ vs. $M_o = 9.6$ μV). No main effects or interactions on posterior P300 amplitude were found for alcohol dependence or ASPD; however, for anterior P300 amplitude a main effect of alcohol dependence was found [$F(1,176) = 7.65$, $p < 0.01$]: individuals with alcohol dependence had lower P300 amplitudes than non–alcohol-dependent individuals ($M_{AD} = 9.5$ vs. $M_{non\text{-}AD} = 11.4$ μV, respectively; Figure 1).

A significant interaction was also found between Age and ASPD [$F(1,175) = 7.60$, $p < 0.01$] for anterior P300

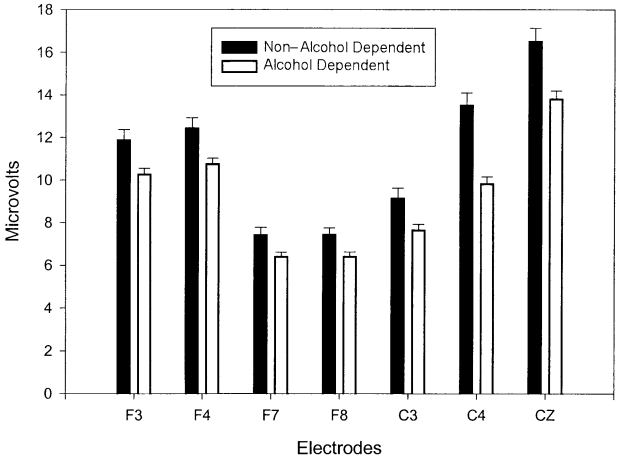

Figure 1. Frontal P300 amplitude (±1 SE) plotted as a function of group (Alcohol Dependent, Non–Alcohol Dependent) and recording site.

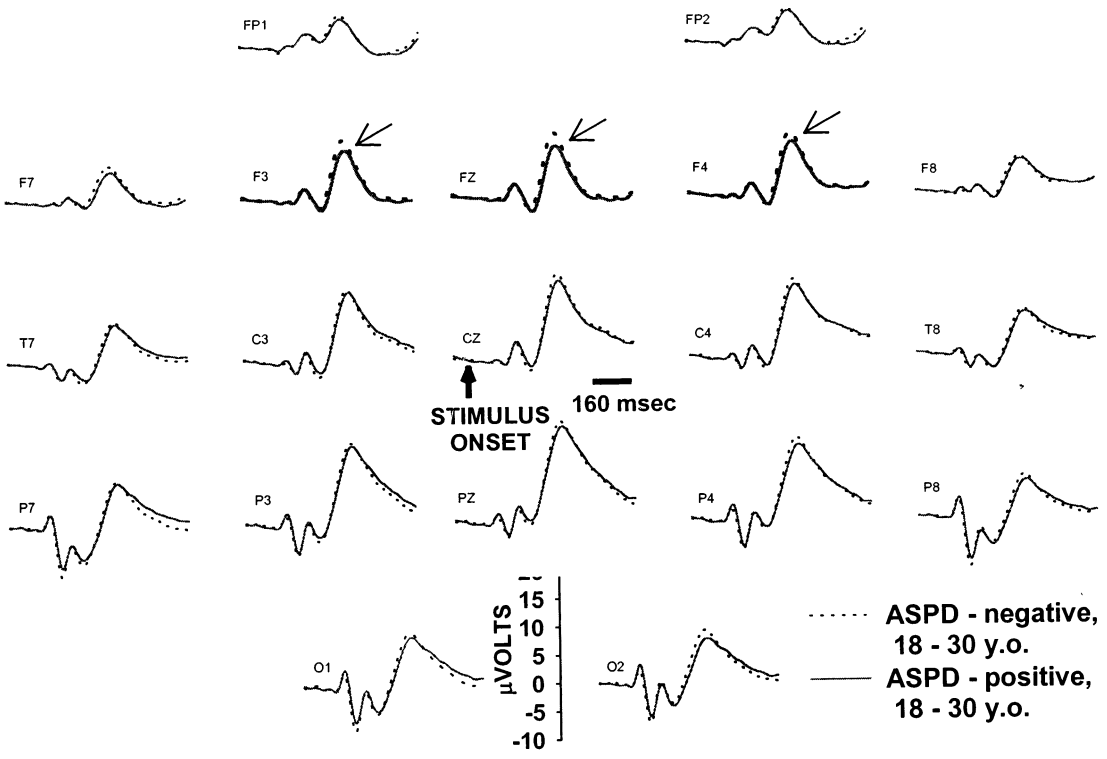

Figure 2. Group-averaged event-related potential waveforms (Alcohol Dependent and control groups combined) elicited by rare target stimuli. Arrow at Cz lead indicates stimulus onset. Note that the difference between antisocial personality disorder (ASPD)-negative and ASPD-positive groups is largest at the F3, Fz, and F4 electrode sites.

amplitude only (Figure 2). Simple effects test revealed that subjects under the median age of 30 years with ASPD had lower P300 amplitudes than those without ASPD [$F(1,190) = 8.00$, $p < 0.005$]. This effect was not found in subjects older than 30. For illustrative purposes, frontal P300 amplitude is presented across finer gradations of age in subjects with and without ASPD (Figure 3). None of the subjects between the ages of 39 and 49 met criteria for ASPD. Therefore, the x axis of Figure 3 does not extend into this age range.

To validate the association between ASPD and anterior P300 amplitude, another analysis was performed in which the total number of conduct disorder/ASPD symptoms reported in the SSAGA was related to frontal P300 amplitude. In the younger group of subjects, this correlation was significant (anterior component: $r = -.154$, $p < 0.01$).

RARE NONTARGET P300S. A main effect of Age was found for posterior P300 amplitude: older subjects had lower P300 amplitudes [$F(1,106) = 3.89$, $p < 0.05$]. No other main effects were found in relation to either posterior or anterior P300 amplitude.

Discussion

We investigated the independent and interactive effects of alcohol dependence, ASPD, and age on P300 amplitude. It

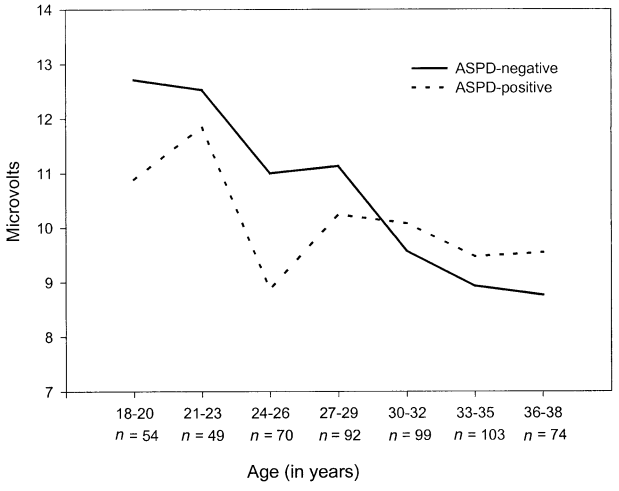

Figure 3. Frontal P300 amplitude for the target and rare nontarget conditions plotted as a function of group (antisocial personality disorder [ASPD]-negative, ASPD-positive) and age.

was hypothesized that alcohol-dependent subjects would exhibit reduced P300 amplitudes particularly at frontal electrode sites. Such a finding would be consistent with a wealth of corroborating data described within the PET, SPECT, and neuropsychologic literatures. The hypothesis was confirmed. Somewhat surprisingly, however, the effects of alcohol dependence on frontal P300 amplitude were not greater in older patients. The absence of a significant alcohol dependence by age interaction may be a consequence of range truncation—that is, no subject was older than 49 years. It is also possible, however, that the neurologic effects of aging and alcohol dependence are truly independent, as several neuropsychologic theorists have suggested (for a review see Oscar-Berman et al 1997).

A second major hypothesis predicted that ASPD would be associated with reduced frontal P300 amplitudes. This hypothesis was also confirmed. Our finding is consistent with previous P300 findings deriving from studies of adolescents with conduct disorder (Bauer and Hesselbrock 1999a), young healthy adults with ASPD (Bauer et al 1994a, 1994b; Hesselbrock et al 1993; O'Connor et al 1994), and cocaine-dependent subjects with comorbid ASPD (Bauer 1997). The frontal focus of the P300 decrement is likewise consistent with demonstrations of frontal PET or SPECT abnormalities among violent criminals (Raine et al 1994, 1998) and among alcoholics with comorbid ASPD (Kuruoglu et al 1996).

The present study demonstrated that the frontal P300 decrement found among ASPD-positive subjects varies with age. A comparable cross-sectional study by Bauer and colleagues (1999a) showed a similar interaction in adolescents. In their study, subjects with conduct problems failed to show a maturational change in frontal P300 amplitude across the age range of 14–20 years. In our study, adults with conduct problems (i.e., ASPD) who were 18–30 years of age also failed to show a maturational change in frontal P300 amplitude (Figure 3). In other words, the evidence provided by these two studies suggests that the frontal brain of individuals with a history of serious conduct problems fails to undergo the normal pattern of maturation. In this context, one could interpret the normal maturation of frontal brain function as initially "unmasking" the effects of ASPD in young adulthood, and subsequently obscuring its effects in middle-aged adults.

Our study might be criticized for interpreting P300 measured at frontal electrode sites. Traditionally, many ERP researchers have focused their analyses only on P300 ERPs recorded at the midline parietal site (Pz); however, the fact that P300 is largest at the Pz electrode cannot be used to support an assumption that P300 is generated in that vicinity (cf. Jayakar et al 1991) or that P300 is a unitary voltage change with a single neuronal generator (for a review see Halgren et al 1998). In fact, a number of recent functional magnetic resonance imaging studies employing P300 task paradigms (Clark et al 1999; Menon et al 1997) have shown that visual and auditory target stimuli evoke significant cerebral blood flow changes in both anterior and posterior brain regions (e.g., anterior cingulate, dorsolateral prefrontal cortex, parietal cortex). Unfortunately, because of the traditional view that P300 should only be measured and interpreted at Pz, researchers have often ignored other brain regions that contribute to P300 amplitude and that are most sensitive to the deleterious effects of alcohol dependence and ASPD.

Our study might also be criticized for ignoring the role of comorbid drug dependence in a subgroup of the alcohol-dependent subjects; however, it should be noted that all of the alcohol-dependent groups, regardless of age or ASPD status, had similar rates of dependence on other drugs (Table 1). Therefore, one might argue that the effects of these drugs were consistent across the alcohol-dependent groups and did not contribute to the variance in P300 amplitude in a systematic manner.

In conclusion, the results of the present study suggest that P300 decrements are not only associated with alcohol dependence but are also present in a subset of individuals with a history of antisocial behavior. The P300 decrements, found at anterior electrode sites only, are suggestive of subtle functional abnormalities in frontal brain regions in alcoholic-dependent individuals and in young adults with ASPD. Further neuroimaging studies are needed to identify the source(s) of the functional deficits in these disorders. In addition, it might be valuable to explore the relationship between these functional abnormalities and treatment response.

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