



Partial recovery of alcohol dependence-related deficits in sleep evoked potentials following 12 months of abstinence

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Stimuli presented during sleep can produce an evoked EEG delta wave referred to as a K-complex. These responses occur when large numbers of cortical cells burst fire in a synchronized manner. Large amplitude synchronized scalp responses require that the CNS contain large numbers of healthy neurons that are interconnected with highly functional white matter pathways. The P2, N550, and P900 components of the evoked K-complex are sensitive measures of normal healthy brain aging, showing a decrease in amplitude with age. N550 and P900 amplitudes are also reduced in recently detoxified alcoholics, most dramatically over frontal scalp regions. The present study tested the hypothesis that the amplitude of K-complex related evoked potential components would increase with prolonged abstinence. Fifteen alcoholics (12 men) were studied twice, separated by a 12 month period, during which time they were followed with monthly phone calls. Subjects were aged between 38 and 60 years at their first study. They had on average a 29.3 ± 6.7 year drinking history and had been abstinent for between 54 and 405 days at initial testing. Evoked K-complexes were identified in the EEG and averaged to enable measurement of the P2, N550 and P900 peaks. Data were collected from seven scalp sites (FP1, FP2, Fz, FCz, Cz, CPz, and Pz). N550 and P900 amplitudes were significantly higher after 12 months of abstinence and an improvement of at least $5 \mu\text{V}$ occurred in 12 of the 15 subjects. N550 and P900 also showed highly significant site by night interactions with the largest increases occurring over prefrontal and frontal sites. The data indicate that the sleep evoked response may provide a sensitive marker of brain recovery with abstinence from alcohol.

Keywords: alcoholism, N550, K-complex, abstinence

INTRODUCTION

Alcoholism is a major health problem with an estimated lifetime prevalence in the United States of approximately 14% (American Psychiatric Association, 2000). Sleep disturbances are ubiquitous in those suffering from alcohol abuse and dependence (Brower, 2003), last long after successful detoxification and have been viewed as a potential pathway to relapse, when alcohol is consumed to facilitate sleep onset (Roehrs et al., 1999). Quantitative markers of sleep physiology may therefore be indicative of severity of alcoholism pathology and may have a causal relationship to heightened relapse risk.

The most consistent sleep finding (Benca et al., 1992) in detoxified alcoholics is a reduction in delta activity measured either as SWS (Allen and Wagman, 1975; Rundell et al., 1975; Wagman and Allen, 1975; Williams and Rundell, 1981; Othmer et al., 1982; Gillin et al., 1990; Le Bon et al., 1997; Drummond et al., 1998; Irwin et al., 2000, 2002; Gann et al., 2001; Feige et al., 2007), or slow wave activity (SWA; Irwin et al., 2000, 2002; Colrain et al., 2009a). Deficient SWS has also been shown to be a predictor of relapse (Brower, 2003). The averaged KC that can be evoked by a stimulus provides a novel experimentally controlled probe of delta EEG production. Its amplitude (N550) is a marker of the ability of the underlying cortex to produce a synchronized response, and thus an indicator

of its functional integrity (Finelli et al., 2001; Crowley et al., 2002, 2004, 2005; Colrain, 2005; Nicholas et al., 2006). N550 and P900 amplitudes and KC incidence are reduced in alcoholics (Colrain et al., 2009b) in a manner that represents an exacerbation of the normal aging effects on these components (Crowley et al., 2002, 2004; Colrain et al., 2010), and is more pronounced at frontal sites.

In addition to being reduced in alcoholics, the N550 has been shown to be correlated with periods of abstinence across subjects but was not related to family history of alcoholism (Colrain et al., 2011). It therefore appears to act as a *state* marker of the pharmacological effects of alcohol use in those with alcohol dependence, and leads to a hypothesis that within individuals, longitudinal data should show increased N550 and P900 amplitudes with abstinence. The hypothesis is further supported by evidence that brain structure demonstrates changes with abstinence (Cardenas et al., 2007) as do aspects of alcoholism-related cognitive and motor decline (Fein and McGillivray, 2007; Yeh et al., 2007), although to varying extents and with variable trajectories (Sullivan and Pfefferbaum, 2005).

The present study sought to determine whether 12 months of abstinence is associated with functional recovery of delta generating ability in sleep EEG.

MATERIALS AND METHODS

SUBJECTS

The present data are drawn from 15 alcohol-dependent subjects (12 men) who had been studied previously (Colrain et al., 2009b). All were followed with monthly phone calls and then restudied approximately 12 months after their initial laboratory visit (mean 394 ± 48 days). Potential participants in the initial study underwent medical and psychiatric screening that included a structured alcohol history (Pfefferbaum et al., 1988) and structured clinical interview (SCID; First et al., 1994). All alcoholic participants met DSM-IV criteria for alcohol dependence, and none had clinically significant sleep disorders based on polysomnographic screening. Eighty-four subjects completed the initial study, 42 with alcohol dependence (27 men) and 42 controls (19 men). The 15 subjects studied a second time after 12 months of abstinence were aged between 38 and 60 years at the time of the first study (mean 52.1 ± 7.2 year). They had on average a 29.3 ± 6.7 year drinking history and had been abstinent for between 54 and 405 days at initial testing (mean 165.3 ± 107.7). Their estimated lifetime alcohol consumption (mean 1283 ± 814 kg) ranged between 603 and 3811 kg for the men and 621 and 1384 kg for the women in the group.

Monthly phone calls and a detailed drinking history taken at the 12 month visit revealed that 13 of the subjects had remained totally abstinent. Of the remaining two, one had a single drink 262 days prior to follow-up, and the other a single drinking occasion 300 days prior to follow-up.

GENERAL LABORATORY PROTOCOL

The protocol for eliciting sleep evoked potentials is outlined in detail in (Colrain et al., 2009b). Briefly, in both the initial and 12 month follow-up studies subjects slept in the laboratory and were exposed to a standard sleep evoked potential protocol. Auditory stimuli consisted of 1000 Hz pure tones presented for 50 ms (2 ms rise time) at 80 dB(A), presented binaurally via E-A-RTONE 3A insert earphones, with a random inter stimulus interval of between 15 and 30 s. A minimum of 200 stimuli were presented in stable stage 2 sleep across a night in the laboratory.

EEG and evoked potential data were recorded from seven scalp sites adapted from the international 10/20 system (FP1, FP2, Fz, FCz, Cz, CPz, Pz), using Grass gold-plated 10 mm electrodes. Two channels of electro-oculogram (EOG) and a submental electromyogram (EMG) were also recorded. All EEG channels were referenced to linked earlobes. Raw data were acquired with a sampling rate of 1 kHz using Neuroscan Synamps[®] amplifiers and stored for offline analysis using Neuroscan Scan[™] software. Signals were continuously displayed in real-time and filtered optimally for visual recognition of sleep stages. Raw EEG data were epoched, time-locked to tone stimuli, and corrected for baseline differences across the pre-stimulus period.

Evoked KCs were defined as per our standard laboratory practice (Crowley et al., 2002, 2004; Nicholas et al., 2002a,b; Colrain et al., 2009b, 2010, 2011) using data from Cz and Fz. The negative peak of the KC had to occur between 400 and 900 ms. after the tone, but no amplitude criterion was used. Epochs containing movement artifacts observed in EOG or EMG channels were discarded. All KC responses within stage 2 sleep were then averaged

for each subject to produce an averaged KC evoked potential at all sites.

Component identification was achieved using Scan[™] software. The P2 component was defined as the most positive peak between 100 and 300 ms post stimulus, the N550 as the most negative value between 400 and 900 ms post stimulus and the P900 as the most positive peak between 800 and 1200 ms post stimulus. Amplitudes were then determined relative to the average of the pre-stimulus baseline. All peaks were determined within all electrode sites.

STATISTICAL ANALYSIS

Data are shown as mean (SD). Repeated measures analysis of variance was conducted to determine whether there were effects of time (initial vs. follow-up) and electrode site (FP1, FP2, Fz, FCz, Cz, CPz, Pz) or time by site interactions. When the assumption of sphericity was violated, degrees of freedom were adjusted using the Greenhouse–Geisser correction, but original degrees of freedom are reported. Relationships between changes in peak amplitude and measures of drinking were evaluated using bivariate correlation analysis.

RESULTS

Grand mean waveforms for all subjects at initial assessment and 12 month follow-up are presented in **Figure 1**.

N550 amplitude was significantly larger at follow-up than at the initial assessment ($F_{(1,12)} = 10.631$, $p < 0.01$). The follow-up amplitude at Fz was at least $5 \mu\text{V}$ larger than that at initial assessment in 12 of the 15 subjects. It displayed a significant effect of electrode site ($F_{(6,72)} = 18.055$, $p < 0.001$), with the typical anterior to posterior gradient. There was a significant time by electrode site interaction ($F_{(6,72)} = 7.310$, $p = 0.005$) indicating that the increase in amplitude occurred only at the anterior sites (see **Figure 2**). N550 latency showed no time, site or time by site interaction effects.

P900 amplitude displayed the same effects as seen for N550 amplitude, with effects of time ($F_{(1,12)} = 8.099$, $p = 0.015$), electrode site (site $F_{(6,72)} = 25.218$, $p < 0.001$), and time by site interaction ($F_{(6,72)} = 8.444$, $p = 0.003$). P900 was larger at anterior sites, larger overall at follow-up, with the increase being more prominent at anterior sites (see **Figure 3**). P900 latency did not vary with time or electrode site.

P2 amplitude displayed a significant effect of electrode site ($F_{(6,72)} = 11.020$, $p < 0.01$) with the typical vertex maximum on both occasions (see **Figure 4**). Follow-up was not significantly different to the initial recording, and there was no time by site interaction. P2 latency also did not vary with time or electrode site.

The magnitude of recovery in N550 amplitude at Fz did not correlate with total estimated lifetime alcohol consumption, the period of abstinence prior to the initial assessment, or the number of years spent drinking. The same negative findings were apparent when only the male subjects were included in the analysis.

DISCUSSION

The results show promising initial support for sleep evoked response as a marker of brain recovery with abstinence. Despite

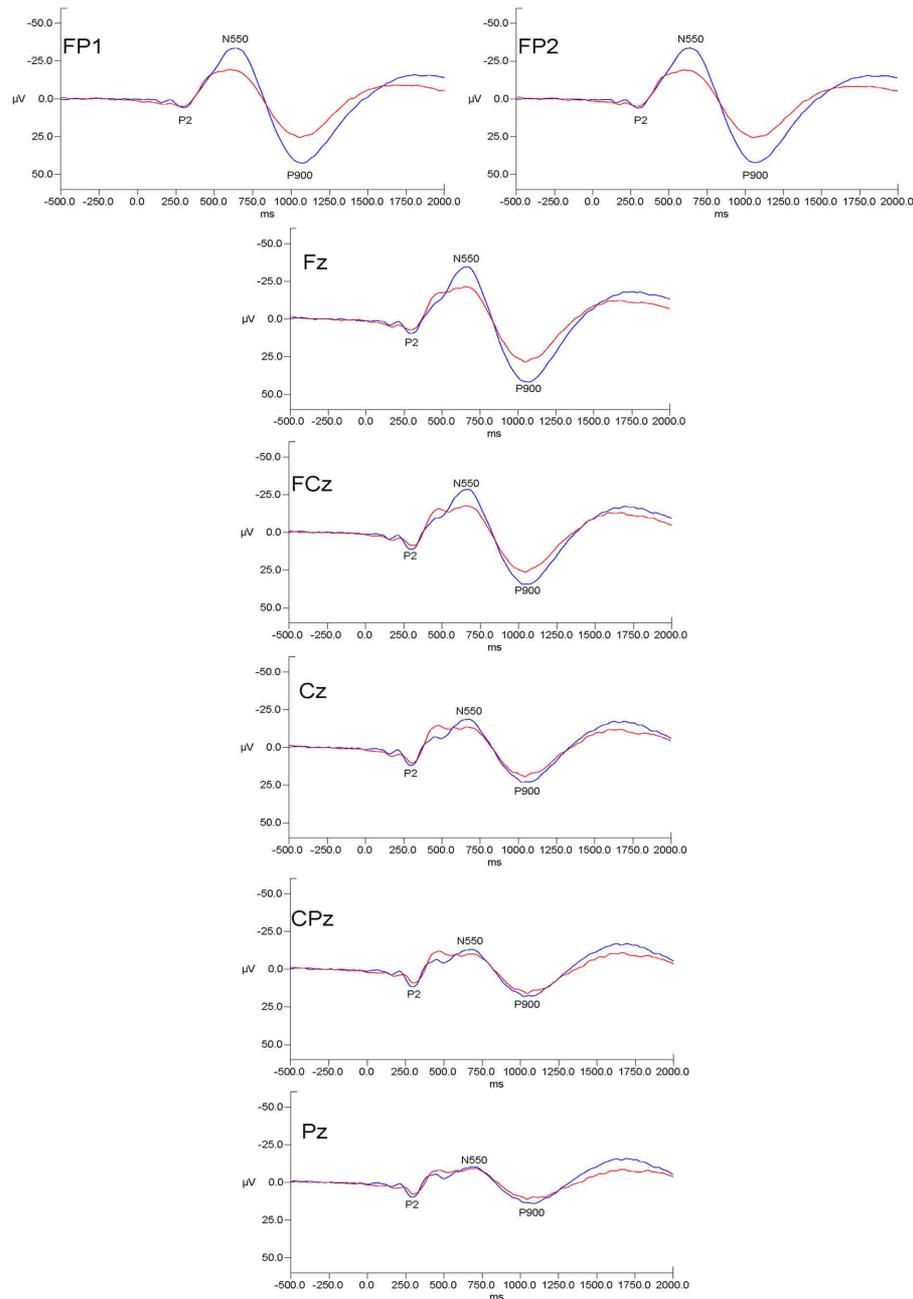


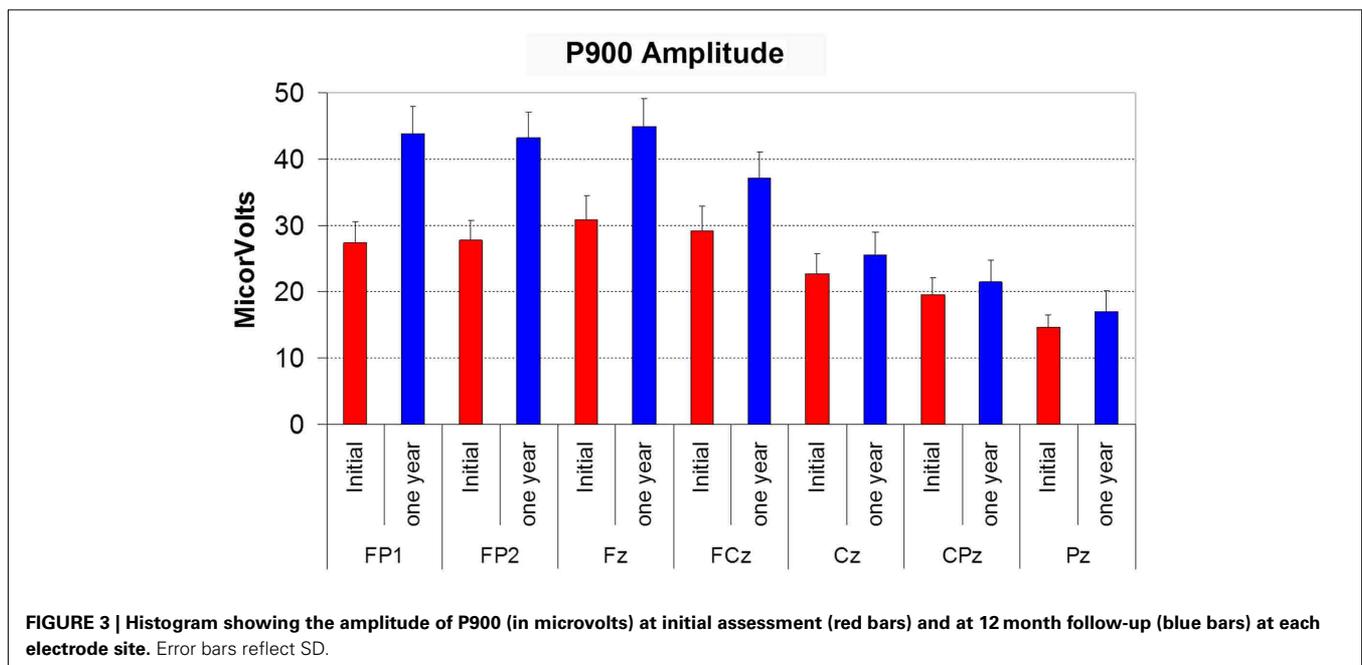
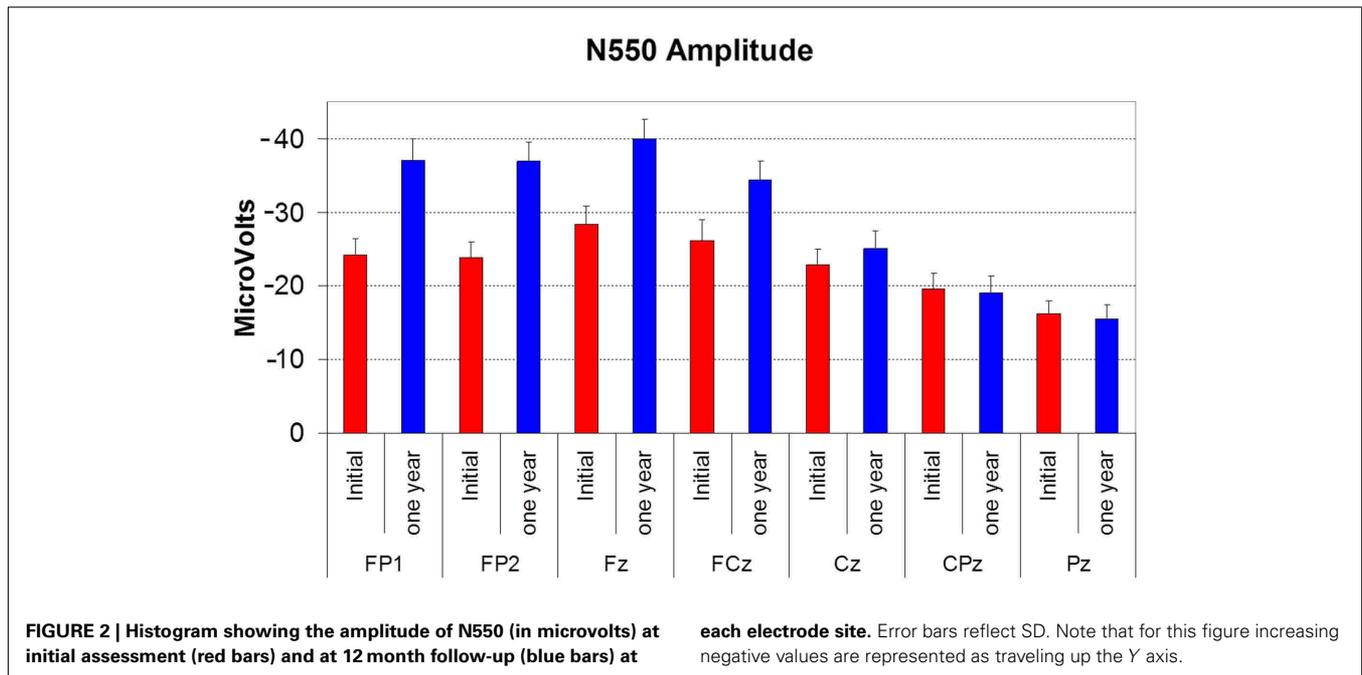
FIGURE 1 | Grand mean evoked potential waveforms for alcoholics at initial assessment (red lines) and at 12 month follow-up (blue lines) for the seven measured electrode sites. Data are presented with negative

voltages up the Y axis. The pattern of results indicates that initial-follow-up differences were prominent over frontal and frontal-polar sites but were diminished at more posterior scalp locations.

small numbers, highly significant results were found showing recovery in N550 and P900 amplitudes at electrode sites in which we have previously shown alcohol dependence-related reductions (Colrain et al., 2009b) and significant relations to MRI measures of brain gray matter volume (Colrain et al., 2011).

It should be emphasized that this apparent partial recovery in delta generation, while a useful functional marker of brain change should not be interpreted as recovery of sleep. Sleep problems

are highly persistent even in long-term abstinent alcoholics and are commonly found to be predictive of relapse (Brower, 2003). We have previously shown that variations in prior length sobriety are not significantly predictive of increased Pittsburgh sleep quality index (PSQI; Buysse et al., 1989) score, decreased SWS, and increased REM in abstinent alcoholics, within the observed range of prior abstinence of between 30 and 719 days (Colrain et al., 2009a).



Abstinence is associated with recovery of structural brain tissue: white matter volume increases with abstinence (Shear et al., 1994; O'Neill et al., 2001) and declines further with relapse (Pfefferbaum et al., 1995). There is less evidence for improvements in gray matter volume (GMV), although Pfefferbaum et al. (1995) reported a trend for increased GMV at 30 days of abstinence. Whole brain tissue volume increases with abstinence (Parks et al., 2002; Gazdzinski et al., 2005; Bartsch et al., 2007), with some evidence that the increase may be greater in alcoholics who are also smokers compared to non-smokers (Yeh et al., 2007). There is some evidence for

a good proportion of the tissue volume increase to occur within the first month or so following drinking cessation (Parks et al., 2002) and for rapid reversal of brain volume gains with resumption of drinking (Gazdzinski et al., 2005). The most extensive study of volumetric changes with abstinence was reported by Cardenas et al. (2007). Abstainers showed between 7 and 12% faster recovery in a number of brain regions. This recovery may underlie the apparent recovery in N550 amplitude given the recent finding of GMV volume accounting for approximately 20% of the variance in N550 amplitude in control and alcoholic subjects (Colrain et al., 2011).

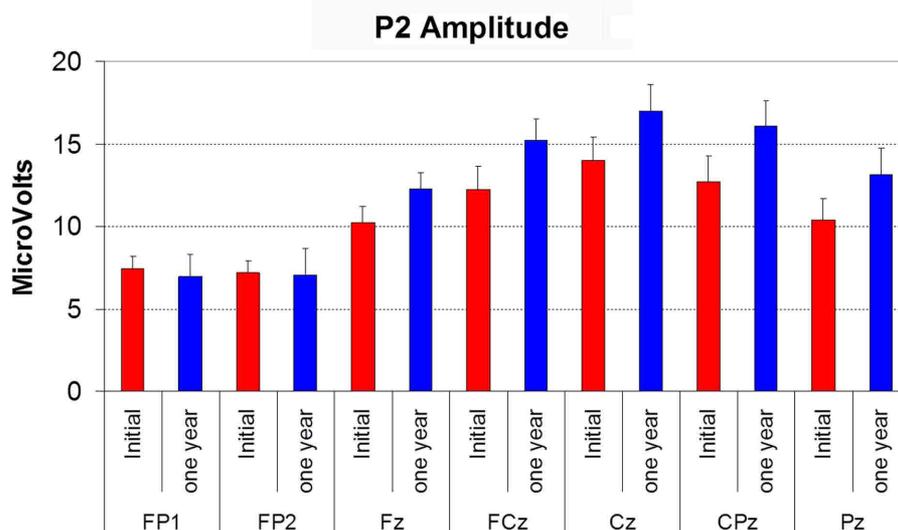


FIGURE 4 | Histogram showing the amplitude of P2 (in microvolts) at initial assessment (red bars) and at 12 month follow-up (blue bars) at each electrode site. Error bars reflect SD.

The study has limitations in terms of the number of subjects observed, and the absence of data from alcoholics who relapsed. Attempts to conduct monthly follow-up by phone were made for all 42 alcoholics from the initial study (Colrain et al., 2009b) with success in 39 cases. Of these 14 relapsed and 25 maintained abstinence. A feature of the disease is that while drinking, alcoholics are unlikely to reliably attend the laboratory, so the study is limited to those abstainers who were sufficiently motivated to re-attend. Nothing definitive can thus be said regarding the possibility that relapsing alcoholics might also have shown a recovery if studied, and more extensive longitudinal assessment of relapsing and abstaining alcoholics is required to address this possibility. Cross-sectional data show N550 and P900 amplitude as lower in older subjects, with regression analysis showing a 1.5 μV decrease per year in N550 at Fz (Colrain et al., 2010). As indicated above, 12 of the 15 subjects displayed at least a 5 μV increase at their 12 month follow-up.

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