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Childhood abuse and EEG source localization in crack cocaine dependence

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ABSTRACT

Fourteen subjects with histories of sexual and/or physical abuse in childhood and 13 matched control subjects were selected from a consecutive series of clients in residential treatment for crack cocaine dependence. Standardized low-resolution electromagnetic brain tomography (sLORETA) was used to estimate the source generators of the EEG in a cortical mask with voxel *z*-scores referenced to normative data at frequency intervals of 039 Hz, with nonparametric permutation to correct by randomization for the number of comparisons and the intercorrelations and variance of distribution of voxel values. Subjects with histories of abuse in childhood had significantly greater EEG power than controls in the theta frequency range (3.51–7.41 Hz), with greatest differences in the 3.90-Hz band distributed mainly in the parahippocampal, fusiform, lingual, posterior cingulate, and insular gyri. The groups did not differ significantly with regard to delta (1.56–3.12 Hz), alpha (7.81–12.48 Hz), beta (12.87–19.89 Hz), and gamma (20.28–35.10 Hz) frequency power. In excess, theta EEG power, a bandwidth of transactions among hippocampus and amygdala and paralimbic and visual association cortex, may be a correlate of childhood exposure to abuse.

1. Introduction

Neurophysiological measures suggest abnormal neurobiology in association with exposure to trauma and abuse, and with substance use disorders. Electroencephalographic (EEG) investigations of posttraumatic stress disorder (PTSD) (Begic et al., 2001; Veltmeyer et al., 2006), as well as a recent systematic review of electrophysiological findings in anxiety disorders (Clark et al., 2009), indicate increased spectral power in the theta bandwidth. These findings appear consistent with observations of increased theta in human subjects during presentation of images of threat (Maratos et al., 2009) or negative arousing stimuli (Balconi et al., 2009), behavioral paradigms designed to elicit anxious rumination (Andersen et al., 2009) or the perception of risk (Qin et al., 2009), during priming involving negative words (Garolera et al., 2007), as well as animal models involving fear memory retrieval (Narayanan et al., 2007a; Pape et al., 2005; Seidenbecher et al., 2003) and immobilization stress (Hegde et al., 2008). These findings suggest a relationship of anxiety to the construct of "hippocampal theta" (Mitchell et al., 2008), which is reduced in humans and animal models by anxiolytic medications including benzodiazepines, buspirone, and pregabalin (Gray et al., 1975; McNaughton and Gray, 2000; Mitchell et al., 2008; Siok et al., 2009).

The reported association of early life stress and abnormal routine EEG (rEEG) (Green et al., 1981; Ito et al., 1993) has been interpreted as indicating temporal-limbic dysfunction characterized as "limbic hyperexcitablity" or frank epileptogenesis (Joels, 2009; Koe et al., 2009; Teicher et al., 2003). Theta range frequency content is strongly represented in temporal lobe EEG epileptiform sharp wave activity (Ebersole and Pacia, 1996), suggesting that some theta range cortical EEG activity may represent a limbic allocortical resonant mode. This concept is supported by a meta-analysis of evoked potential (EP) data in PTSD that found increased prevalence of P200 augmenting response to progressively louder auditory stimuli (Karl et al., 2006), suggesting a theta range frequency neural resonance consistent with the concept of the EP as entrained EEG resonance, particularly in the theta band (Basar et al., 1998; Sakowitz et al., 2005).

Studies focusing on a history of abuse or trauma as an independent variable have commonly controlled for an effect of substance abuse by excluding patients with substance use disorders. However, given the association of substance abuse with histories of abuse or trauma in childhood (Bennett and Kemper, 1994; Briand and Blendy, 2010; Triffleman et al., 1995), it is clinically relevant to include subjects with histories of substance use disorders. Previous work in this laboratory indicates persistently abnormal quantitative EEG (QEEG) findings in crack cocaine dependence (Alper, 1999; Alper et al., 1998, 1990; Prichep et al., 1996, 1999, 2002). A decrease in delta absolute EEG power has been

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observed that is most prominent in anterior leads (Alper et al., 1990; Prichep et al., 1996, 1999), persists for at least 6 months in drug-abstinent patients in long-term residential treatment (Alper et al., 1998), and has been hypothesized to relate to stimulant sensitization (Alper, 1999).

The present study utilized source modeling to identify the mathematically most probable sources of the scalp-recorded EEG in a three-dimensional cortical mask (Pascual-Marqui, 2008) to compare two groups of subjects in residential treatment for crack cocaine dependence. Within this population, subjects with a history of physical or sexual abuse in childhood were compared with control subjects without histories of abuse but otherwise matched to index subjects with regard to substance use and demographic variables. Comparisons were computed across the entire set of voxels comprising the mask as an alternative to the a priori definition of regions of interest (ROIs). Nonparametric permutation tests (Nichols and Holmes, 2002; Pascual-Marqui, 2008) were used to correct for the number of comparisons by randomization, which addresses the high intercorrelations among voxels and relatively much smaller number of underlying dimensions of the QEEG voxel data set (Andresen, 1993), as well as the variance of the distribution of voxel values.

2. Methods

The Institutional Review Board of the New York University School of Medicine approved this research. All subjects provided written informed consent.

2.1. Subjects

Subjects were recruited from consecutive admissions in the context of ongoing research funded by the National Institute on Drug Abuse at the New York City Induction Facility of Phoenix House (PH), a large drug-free residential therapeutic community (Alper et al., 1998; Prichep et al., 1996, 1999). Subjects were tested 5–14 days after the last reported use of cocaine. All PH facilities are locked, and random urine testing is also obtained to verify abstinence while in the program.

A psychiatrist interviewed all patients prior to entry into the study and utilized the Structured Clinical Interview for DSM-III-R (SCID) to assess the categorical diagnosis of cocaine dependence and other substance use disorders. Ratings were obtained utilizing the Hamilton Depression (Hamilton, 1980) and Anxiety (Hamilton, 1959) Scales, the Beck Depression (Beck et al., 1961) and Anxiety (Beck et al., 1988) Inventories, and the Minnesota Cocaine Craving Scale (Halikas et al., 1991).

The inclusion criteria for all subjects were as follows: fulfilling DSM-III-R criteria for cocaine dependence for at least 1 year and strongly preferring crack cocaine to any other substance; no history of ever having met DSM-III-R criteria for dependence on any substance other than cocaine and alcohol; alcohol intake limited to non-dependence levels in the year preceding admission; negative urine screening for other drugs including heroin, barbiturates, amphetamine, and phencyclidine; and estimated IQ > 80. Subjects were excluded that had a history of head trauma with loss of consciousness or significant neurological or medical condition including any history of seizures regardless of an association with drug abuse, intravenous drug use, evidence of HIV infection or self-report of a positive HIV serology, or treatment with medically prescribed psychotropic medications within 60 days of intake.

Abuse histories were obtained (see below) from 50 consecutive subjects with crack cocaine dependence. Fourteen of these 50 subjects reported histories of abuse in childhood as defined below; seven subjects reported only sexual abuse, four reported only physical abuse, and three reported. From the remaining 36 subjects, a control group of 13 subjects was selected that matched the abused set of subjects with regard to age, gender, years of education, substance use history and clinician- and self-administered ratings of mood and anxiety as summarized in Table 1. *t*-Tests and Fisher exact tests were used to confirm the lack of significant differences between the two subject groups. The selection of the study groups was blind with regard to electrophysiological data.

2.2. Assessment of history of abuse in childhood

Childhood histories of abuse were obtained using an approach developed and previously utilized in research on conversion disorder (Alper et al., 1993, 1997; Sharpe and Faye, 2006). Abuse was regarded as having occurred in childhood if the victim had been 18 or younger at the time of the abuse. Criteria for sexual abuse included coercion, or household or family membership of the perpetrator. In the case of non-coercive sexual activity with a non-household member before age 14, a 5-year or greater positive age difference between the perpetrator and the patient was regarded as indicating abuse. Sexual acts were defined as any purposeful attempt at physical contact by the perpetrator with the patient's anogenital region or breasts or attempt to engage the patient in sexual contact with the perpetrator. By "purposeful" it is meant that the actions of the perpetrator, if unopposed, would directly result in sexual contact.

Physical abuse was defined as violence deliberately inflicted on a patient during childhood in a context in which the patient was unable to actively defend him or herself by virtue of the physical advantage or parental authority of the perpetrator. The physical act was required to have clearly exceeded existing cultural norms regarding the disciplining of children.

2.3. EEG data acquisition

Twenty minutes of eyes closed resting EEG data while they were collected from subjects while and seated comfortably in a light attenuated room. Electrodes were placed on the standard 19 electrode sites of the International 10/20 system referenced to linked earlobes. A differential eye channel was used for the detection of eye movement. EEG technicians monitored the patient throughout the recording, to minimize artifact and help to maintain alertness. All electrode impedances were below 5000 Ω. The EEG amplifiers had a bandpass from 0.5 to 70 Hz (3 dB points), with a 60-Hz notch filter. Data were sampled at 100 Hz.

Forty-eight EEG epochs of 2.56 s each were selected for quantitative analysis from 20 min of continuous raw EEG. Data were determined to be artifact-free based on visual inspection, with the assistance of a computerized artifact-detection algorithm. A Fast Fourier Transform (FFT) was used to derive 87 very narrow bands (VNB), equally spaced 0.39-Hz-width frequency bands centered at frequencies from 1.56 Hz to 35.1 Hz. Conventional broad bandwidths were defined as follows: delta, 1.56–3.12 Hz; theta, 3.51–7.41 Hz; alpha, 7.80–12.48 Hz; beta, 12.87–19.89 Hz; beta 2/gamma, 20.28–35.10 Hz. Bands below 1.56 Hz were removed in order to minimize artifact due to eye movement. Higher coefficients were truncated at the 3-db attenuation point for anti-aliasing acquisition filtering.

2.4. EEG data analysis utilizing standardized low resolution electromagnetic brain tomography (sLORETA)

This study utilized sLORETA (Pascual-Marqui, 2002, 2008), a standardized, discrete, distributed, linear, minimum norm inverse solution for estimating the source generators of the scalp-recorded EEG. The standardization used in sLORETA represents an improved alternative to the use of a smoothing algorithm (Pascual-Marqui et al., 1994), and provides mathematically exact localization to test point sources (Pascual-Marqui, 2009) which receives independent support by investigations utilizing idealized mathematical models (Greenblatt et al., 2005; Sekihara et al., 2005; Wagner et al., 2004).

Table 1
Variables on which subjects with histories of abuse in childhood and control subjects were matched. *t*-Tests and Fisher exact tests were ($p \leq 0.05$) used to confirm the lack of significant differences between the two subject groups.

Variable	(+) History of abuse in childhood	(−) History of abuse in childhood	*p*
N	14	13	
Age (years)	30.8 ± 4.3	30.8 ± 4.5	0.15
Gender (M/F)	6/8	6/7	0.86
Years of education	11.4 ± 1.2	12.5 ± 5.7	0.07
Age of first use (years)	23.2 ± 5.2	25.4 ± 5.7	0.31
Years of crack or cocaine use	9.7 ± 4.0	11.5 ± 6.3	0.38
Years of crack use	7.5 ± 3.2	7.3 ± 4.3	0.90
Previous year crack use (g/year)	231.8 ± 287.8	120.0 ± 108.3	0.22
Age of first alcohol use	14.7 ± 3.9	16.9 ± 7.1	0.38
Years of alcohol use	15.9 ± 9.2	15.2 ± 11.4	0.90
Previous year alcohol use (units)	472.3 ± 99.1	305.3 ± 388.6	0.48
Minnesota Cocaine Craving Scale	3.2 ± 4.0	3.1 ± 2.5	0.89
Beck Depression Inventory	14.4 ± 8.5	12.2 ± 8.8	0.50
Hamilton Depression Scale	10.9 ± 4.6	13.8 ± 6.5	0.19
Beck Anxiety Inventory	7.3 ± 7.8	4.3 ± 3.7	0.22
Hamilton Depression Scale	6.7 ± 4.9	8.8 ± 8.4	0.43