

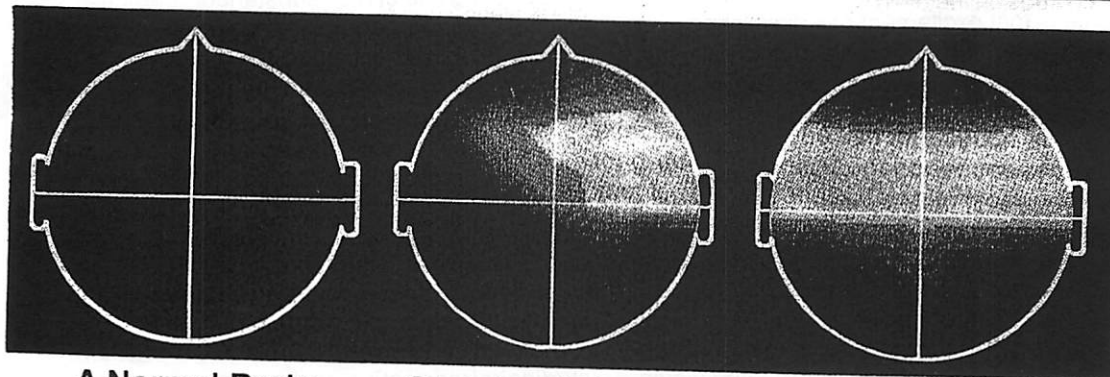
# CLINICAL EEG

ELECTROENCEPHALOGRAPHY



## SUPPLEMENT

Substance Use Disorder Exacerbates  
Brain Electrophysiological Abnormalities  
in a Psychiatrically-Ill Population



A Normal Brain

Chemical Imbalance  
in Depressed  
Patients

Depression Plus  
Brain Injury From  
Drug Abuse

## Editorial

### Quantitative EEG and Substance Abuse

As I write this editorial introducing a supplement to the October issue dealing with quantitative EEG (QEEG) changes associated with substance abuse, I am looking at a small strip of paper recently given to me by Dr. Charles Henry. It is a portion of a single-channel EEG recorded on ticker tape in 1939, and we are considering how and where to display and preserve it, perhaps on the Offner instrument first used by Dr. Milton Parker to record EEGs at Ohio State in 1946, now stripped of its galvanometers but handsomely stained and polished. These artifacts and others like them no doubt in the possession of many readers remind us of a time when electroencephalography promised to reveal many exciting secrets of normal and abnormal brain function. First in the hands of Hans Berger and then in the laboratories of Frederic and Erna Gibbs as well as the other EEG pioneers, alterations in the morphology, frequency, and eventually topography of EEG signals promised better understanding and more accurate diagnosis of neurological and psychiatric disorders, and seemed to offer a way to measure the effect of drugs on the brain.

Some of that excitement has diminished over the past half century, as the diagnostic palm has passed to some degree from EEG to imaging modalities, first computed tomography and then magnetic resonance, and now SPECT and PET and functional MRI. The principal remaining advantages for EEG and related tests are relative ease and cheapness of administration, and well-documented sensitivity, particularly in patients with epilepsy, to functional alterations that have no counterpart in altered brain structure. One might think that fairly inexpensive tests that could be quickly conducted and readily repeated would find great favor at a time of financial constraint and cost containment in medicine. Moreover, theoretical tools for processing and transformation of the EEG signals in various ways have been available for some time, and the computer revolution that has so comprehensively transformed modern medicine might be expected to facilitate the extraction from complex brainwaves of patterns and changes that are not as rapidly or easily grasped by the unaided eye. It is a great irony indeed that, as the Decade of the Brain draws to

its close, the role of the fastest and cheapest measure of brain function in an outpatient setting is a matter of doubt, and as the Century of the Computer reaches its end, the application of computer techniques to electrodiagnosis is a matter of controversy.

The regular reader of Clinical EEG will know that issues of sensitivity and specificity in EEG and evoked potentials are regularly dealt with. The potential perils of QEEG techniques, particularly in psychiatric and neurodevelopmental applications, have also been discussed in these pages. It is nevertheless exciting to see neurophysiology generally and QEEG particularly advance to a point from which it may have some influence on defining and solving the problems of the day. Dr. Braverman's work with Dr. Blum gives new meaning to the concept of cerebral dysrhythmia as a medical disorder of the brain which is exacerbated by drug abuse.

There is probably no reader, in the United States or elsewhere, who is not aware of the medical, economic, social and political aspects of escalating use of illicit substances, particularly among young people. It is generally agreed that neurologic examination, CAT scan, and MRI imaging are of limited value in measuring the effects of substance use and abuse, short of long-term systemic consequences or catastrophic complications. Despite much work in this area, standard EEG and evoked potentials are also of limited value. There is increasing evidence, much of it in this journal, that QEEG techniques improve neuropsychiatric diagnosis and facilitate psychotropic drug treatment. Drs. Eric Braverman and Kenneth Blum have, in extensive studies retrospective and prospective over a seven-year period, shown QEEG changes not evident in other clinical and imaging modalities in patients with substance abuse problems not yet attended by long-term complications, in whose care education and rehabilitation are still possible and crucially important. Such findings suggest that QEEG may be a cost-effective adjunct in the evaluation, treatment, and education of substance-abusing patients. As the problems of drug abuse and its consequences are the focus of increasing concern in our society,

**Pictorial Proof of Brain Damage Caused by Drugs**  
**Published in *Clinical EEG***  
**Eric Braverman, M.D. & Kenneth Blum, Ph.D.**

**RESPONSE**

**David Smith, M.D.**

**President, American Society of Addiction Medicine**

**Founder & President, Haight/Ashbury Free Clinics, Inc., San Francisco**

- *"The Braverman and Blum study, I think, will be a very important breakthrough in strengthening our scientific basis of addiction medicine"*
- *"The study identifies in a very graphic form, the nature of the biological basis of addiction"*
- *"The photographs developed by Braverman and Blum will help young people in perceiving high risk in experimenting with potent psychoactive drugs, such as alcohol, cocaine and marijuana"*
- *"The study is very significant because it establishes a much better understanding of the electrophysiological brain function as measured by EEG/BEAM in individuals, both predisposed to addiction and those who have comorbidity with depression and substance use disorder"*
- *"Using this new technology, especially the visualization of this brain dysfunction, will not only help science but will also help prevention and treatment"*
- *"The Braverman and Blum study is a stepping stone and will have great impact as a monitoring device in assisting clinicians in terms of observations related to treatment progress in the addict"*
- *"Proper utilization of the photographs developed by Braverman and Blum could have significant impact in affecting those young people having comorbidity with depression and substance use disorder, potentially preventing teenage suicide"*
- *"In summary, in a certain sense, a picture is worth a thousand words"*



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June 23, 1999

To whom it may concern:

Alan Walden, D.C., C.Ad., has been working in the detox department of the Haight Ashbury Free Clinics. A chiropractor, Dr. Walden is also trained and Board Certified by the American College of Addictionology and Compulsive Disorders. He renders subluxation-based chiropractic care using Dr. Jay Holder's Torque Release Technique and protocols.

For many years this clinic has introduced many innovative strategies in addiction treatment. Patients are responding favorably to non-force chiropractic care.

Peace and Health,

David E. Smith, M.D.  
President & Founder  
President, American Society of Addiction Medicine  
DES/mz

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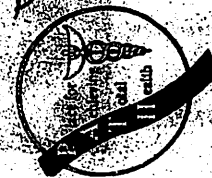
*"As a board member of the PATH Foundation,  
I am looking forward to my participation in the  
upcoming conference in San Francisco.  
And with a keen interest in addiction research  
related to the brain, I also look forward to my  
continuing personal participation in ongoing  
research studies."*

*Nick Nolte*

*A  
historical  
event  
is  
about  
to  
take  
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*and  
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Unlike other scientific meetings, the purpose of this conference is to bring leading scientists and well-known celebrities such as Nick Nolte, the conference spokesperson, face-to-face to discuss openly their affliction.

The total cost of the conference is only \$295 (tax deductible). This includes a one-day scientific session (from 8:00 AM to 11:00 PM). **You will also enjoy a once-in-a-lifetime Luncheon and Press Conference with Nick Nolte and the scientific speakers.**

*We are looking forward to spending this historical day with you!*

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**Synopsis**

**T**his conference will present new evidence that supports involvement of the dopamine D2 receptor and of other genes: in reward, addiction vulnerability and in the emerging concept "Reward Deficiency Syndrome." It will serve as a stepping stone for discussions of targeted treatment approaches to reward-deficiency disorders, which may afflict as many as 88 million individuals in the United States. We will discuss genetic involvement and the dramatic importance of nature (as well as nurture) in addictions to alcohol, opiates, psychostimulants, nicotine, cannabis, pathological gambling, sex, violence and foods. Clinical and genetic correlates, evolving traditional and alternative medical treatments, behavioral and electrophysiological approaches, and dietary avenues will be presented.

**Focus**

**T**his conference will focus, in a one-day meeting, on unbiased 30-minute presentations of data by leading scientists in the field followed by discussion and dialogues with well-known individuals about the problems faced by those with such genetic antecedents. Presentations will be geared for both scientific rigor and clarity for the public. An evening session will focus on potential clinical aspects.

**Speakers**

Daniel G. Amen, M.D.  
Kenneth Blum, Ph.D.  
Michael Bozarth, Ph.D.\*  
Eric Braverman, M.D.  
Wesley Clarke, M.D., Ph.D., J.D.\*  
Eliot Gardner, Ph.D.  
Shirley Hill, Ph.D.  
Jay M. Holder, D.C., C.Ad.  
Kathleen Kantak, Ph.D.  
Theresa Kosten, Ph.D.  
Joel Lubar, Ph.D.  
Barry McCaffrey, General\*  
Richard Milestein, Ph.D.\*  
Ernest P. Noble, Ph.D., M.D.  
Nick Nolte  
Julia Ross, M.D.  
Richard Seymour, Ph.D.  
David E. Smith, M.D.  
George Uhl, M.D.  
Nora Volkow, M.D.  
Roy Wise, Ph.D.

The Amen Clinic for Behavioral Medicine, Fairfield, CA  
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Conference Co-Chairperson: Ernest Noble  
Scientific Co-Chairpersons: George Uhl and  
Nora Volkow  
Clinical Co-Chairpersons: Eric Braverman and  
David E. Smith  
Conference Spokesperson: Nick Nolte

this may be an area in which clinical neurophysiology can beneficially impact a major public health problem, as Berger, the Gibbsses, and so many others attempted to do.

This prospect should be exciting to electroencephalographers. Because of this excitement and the timeliness of the subject, we published the Braverman and Blum study in an expedited fashion, as a supplement so that color graphics would be readily visible to all. We hope that this

timely contribution will draw attention to our discipline and journal, and to the promise of pharmacoelectroencephalography for modern neuropsychiatry. Finally, we are grateful to Dr. David Smith, President of the American Society of Addiction Medicine, for putting this work in the perspective of current addiction research and treatment. This supplement may be the beginning of fruitful collaboration between clinical neurophysiology and clinical addictionology.

Miles E. Drake, Jr., M.D.  
Chief Editor  
Clinical Electroencephalography

In the last five years there has been a surge in substance abuse amongst teenagers in the United States. Unfortunately this increase parallels expanding scientific knowledge about the damaging effects of drugs on brain function. The Braverman and Blum study identifies increased electrophysiological disturbances in substance abuse disorder subjects. They correlate such dis-

turbances with genetic evidence suggesting a premorbid existence of brain dysfunction making the subjects more susceptible to the disabling effects of drug abuse. Such research has important implications for better understanding of the biological basis for the disease of addiction as well as providing a stronger scientific basis for prevention and early intervention for high risk individuals.

David Smith, M.D.  
President of the  
American Society of Addiction Medicine  
Founder and President of the  
Haight/Ashbury Free Clinics, Inc.



# Substance Use Disorder Exacerbates Brain Electrophysiological Abnormalities in a Psychiatrically-Ill Population

Eric R. Braverman and Kenneth Blum

## ABSTRACT

**Objective:** To assess by brain electrical activity mapping whether cocaine and alcohol abuse and dependence would exacerbate electrophysiological abnormalities in a psychiatrically-ill population.

**Design, Setting, and Participants:** Utilizing a brain mapping system, we assessed EEG, Spectral Analysis (Quantitative EEG(QEEG)), Evoked Potentials (Auditory and Visual), and P300 (cognitive evoked potential), in a total of 111 probands divided into three groups: controls (N = 16), psychiatrically-ill without comorbid substance use disorder (N = 34), and psychiatrically-ill with comorbid substance use disorder (cocaine and alcohol abuse and dependence) (N = 61), at an outpatient neuropsychiatric clinic. With regard to demographic data, the group participating in this study did not differ significantly. A comparison was made among the groups to assist in differentiating the effects of substance use disorder compared to psychiatric disease on brain electrical activity.

**Main Outcome Measures:** An assessment of electrophysiological abnormalities and their brain location in psychiatric and substance use disorder patients was done with a brain electrical activity mapping test.

**Main Results:** Among the non-substance use disorder, psychiatrically-ill (PI) and substance use disorder, psychiatrically-ill (PI/SD) groups, significantly different brain map abnormalities were observed relative to an assessed normal population MANOVA ( $P = .017$ ). Moreover, with regard to Spectral Analysis, ANOVA was significant at a  $P = .038$ , and we found a weighted linear trend of increased abnormal total spectral analysis ( $P = .0113$ ), whereby substance use was significantly worse than controls. Moreover among the PI and PI/SD groups, significantly greater total evoked potential (EP) brain map abnormalities were observed when compared with a characterized normal population ( $P = .0023$ ) with increasing abnormalities as a function of sub-

stance use disorder as measured by a weighted linear trend ( $P = .0022$ ). In order to determine the site of the EPS abnormalities, we evaluated these abnormalities by location. In this regard, we found all temporal abnormalities (AVBITA, see Table 2) among the PI and PI/SD groups to be significantly greater relative to an assessed normal population ( $P = .0026$ ). Furthermore, we observed a linear trend of increased temporal abnormalities with increasing substance use disorder ( $P < .0008$ ). In terms of bitemporal abnormalities (AVBIT) among the PI and PI/SD groups, we also found significantly more bitemporal lobe abnormalities in the PI/SD group compared to our control population ( $P = .009$ ). Additionally, a weighted linear trend of increased abnormal bitemporal lobe abnormalities was observed with increasing substance use disorder ( $P = .0022$ ). In the frontal lobe similar findings were observed. With AVBIFA the ANOVA was  $P < .011$ , with a weighted linear trend of  $P < .005$  and the PI/SD group were significantly more abnormal than PI or CS on a Duncan Range test.

It is noteworthy that in a selected group of depressed (Major Depressive Disorder Recurrent, 296.3) patients, we found profound abnormalities in the various brain map parameters tested. MANOVA and Univariate ANOVA's revealed significantly greater abnormalities in the PI and PI/SD groups compared to assessed controls. A MANOVA for total brain abnormalities was significant at  $P = .043$  and univariate ANOVA's for composite measurements of TSA ( $P = .017$ ), EPS ( $P = .0002$ ), AVBITA ( $P = .000015$ ), and AVBIT

---

Eric R. Braverman, M.D., is from the Department of Psychiatry, New York University School of Medicine, New York, New York, and the PATH Foundation, Princeton, New Jersey. Kenneth Blum, Ph.D., is from the Department of Behavioral Sciences, University of Texas, Houston TX, School of Public Health at San Antonio, Texas, and the PATH Foundation, Princeton, New Jersey.

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( $P < .00002$ ) are also significant. With regard to EPS and AVBIT a weighted linear trend was observed where there were increasing abnormalities with increasing substance use disorder,  $P = .0001$  and  $P = .000003$ , respectively. Most importantly we found that in addition to increased abnormalities with increasing substance use disorder the PI/SD group had significantly more abnormalities compared to the PI group with regard to both the TSA ( $P < .05$ ) and AVBIT ( $P < .05$ ) composite parameters as measured by a Duncan Range test. Additionally, we found increased abnormalities in EPS in the frontal (but not occipital and parietal) lobes, AVBIF ( $P = .0116$ ) and AVBIFA ( $P = .0116$ ), of both the PI and PI/SD groups, where PI/SD groups had more abnormalities relative to PI and CS in our total population as well as the select depressed group, with a weighted linear trend of  $P = .0054$  and  $P = .0065$  respectively.

**Conclusion:** Comorbid substance use disorder in psychiatric probands (especially in depressed patients) significantly exacerbates a potential premorbid vulnerability, and suggests a gene-environment interaction which leads psychiatrically-disturbed individuals with substance use disorder to worsen their brain dysfunction, particularly in the bitemporal regions of the brain.

## INTRODUCTION

This study of substance use disorder utilizes QEEG or spectral analysis and evoked potentials topographically mapped, and demonstrates significant electrophysiological abnormalities in an outpatient clinical neuropsychiatric setting.

Brain electrical activity mapping, including QEEG and cortical evoked potentials, has revealed the existence of subtle neurological changes in a wide variety of subjects<sup>1</sup>, including schizophrenics,<sup>2-6</sup> criminals,<sup>7,8</sup> depressives,<sup>9</sup> Alzheimer's,<sup>10,11</sup> toxic exposures,<sup>12-14</sup> metabolic encephalopathy,<sup>15</sup> AIDS,<sup>16</sup> attention deficit disorder and their response to medication,<sup>17-19</sup> and alcoholism and drug abuse.<sup>20-37</sup> Well-developed criteria for utilization of brain electrophysiological mapping has therefore been established for psychotic or affective disturbances and impulse control disorders, as well as other organic behavioral disorders.<sup>20-38</sup> Moreover, the American Psychiatric Association Task Force recently embraced the utilization of brain electrical activity mapping as a promising technique for elucidating brain illnesses (see review by Duffy et al).<sup>39,40</sup> Visual interpretation of EEG patterns of psychiatric patients in actuality may in the future be passé.<sup>41-42</sup>

The rationale for the present investigation stems from several previous studies that have demonstrated changes in EEG,<sup>20-23</sup> spectral analysis,<sup>24,25</sup> evoked potential (i.e. auditory evoked response),<sup>25-32</sup> P300,<sup>31-35</sup> as well as neuropsychological deficits<sup>36,37</sup> in a variety of substance use disorders and children at risk for these disorders. These studies, although suggestive, were generally comprised of a small number of subjects and did not systematically include a full spectrum of comorbid electrophysiological parameters tested in psychiatric patients with and without substance use disorder.

However, many authors have reported findings of increased paroxysmal EEG changes in a variety of psychiatric patients with an observed treatment response to anticonvulsants.<sup>43-45</sup> Others claim that the electroencephalographic differences of psychiatric patients from the normal population may be explained by drug effects, metabolic disturbances, or brain injury.

It is well known that drugs can induce neurotransmitter deficits in the deep limbic structures (located in the temporal lobe),<sup>46,47</sup> leading to focal electrophysiological abnormalities. Those topographical changes may be an important marker or component which motivates an individual's desire to engage in substance use. Ballenger and Post<sup>48</sup> have suggested that the kindling phenomenon of the limbic system may be a factor in both the craving and withdrawal of substance use disorder subjects. Moreover, Goldstein and colleagues reported on the importance of kindling (kindling refers to the tendency of some brain areas to react to repeated low-level electrical stimulation by progressively boosting electrical discharges and thus lowering seizure thresholds)<sup>47-49</sup> in endogenous depression, which may be exacerbated by substance use disorders.<sup>49,50</sup> In one study of substance use disorders comorbid psychiatric disorder was found to be as high as 70-90%.<sup>51</sup>

Gerez and Tello<sup>52</sup> have provided specific evidence that supports the kindling model of drug-seeking behavior. They found that structural abnormalities and/or neuropsychological abnormalities were observed in only those individuals with focal topographical changes. Moreover, they found that focal EEG and evoked potential changes predicted good response to anticonvulsants, while the presence of epileptiform (EEG) activity without focal changes did not. Focal evoked potential abnormalities probably have a clinical utility in predicting anticonvulsant responsive treatment in the substance use disorder sub-

jects as well. In this regard, over two decades earlier, anticonvulsants were explored as potential withdrawal agents, especially in the treatment of alcoholism. More recently, Halikas et al.<sup>53</sup> first used the iminostilbene derivative carbamazepine to reduce craving response of severe cocaine abusers,<sup>54</sup> possibly by lowering seizure threshold as suggested by Mott and associates in children predisposed to seizures.<sup>55</sup> Additionally, Stuppaek and co-workers<sup>56</sup> have suggested that carbamazepine (CBZ) may be used as the drug of choice in non-delirious alcohol withdrawal. However, the response to CBZ treatment has been variable, as evidenced by negative studies,<sup>57</sup> which may suggest subpopulations of responsive or unresponsive cases, possibly based on both genetic and electrophysiological disturbances which can be identified by standard electrophysiological activity mapping.

Since epileptic-like foci<sup>52</sup> are detected in the absence of epileptiform-like activity by spectral analysis (coefficient of variation for each band), and by changes in the evoked potential, we investigated topographical changes in patients with substance use disorders which might help characterize these individuals for treatment. Furthermore, due to a lack of systematic data on a multitude of electrophysiological parameters in substance use disorder subjects, a definitive study characterizing a widespread presence of electrophysiological disturbance in a psychiatric population seemed warranted. Moreover, comorbidity of psychiatric disease in substance use disorder populations has now been well established.<sup>58,60</sup> Therefore, we decided to electrophysiologically map and compare a substance use disorder population with comorbid psychiatric disease to non-substance use disorder controls with no significantly different psychiatric diagnoses. Our primary goal was to differentiate potential exacerbation of electrophysiological abnormalities and their location in a substance use disorder and psychiatrically-ill population.

## SUBJECTS AND METHODS

A total of 111 subjects (107 white, 2 Asian, and 2 black) were selected for study from approximately 5,000 visits from 800 patients to an outpatient private clinical practice (Medical and Neuropsychiatric) and research foundation in Princeton, New Jersey, in a one-year period. The subjects entered assessment through word of mouth, physician referral, and media announcements. These patients were highly motivated for compliance, since services provided by the clin-

ic were costly, and they were informed that results and future treatment would be optimized by a brain map taken in a drug-free patient. All subjects in the substance use disorder group were clinically established to have had early full (DSM IV) remission of substance use disorder.<sup>61</sup> The demographic breakdown of our sample base is described in Table 1. Age, gender, and psychiatric diagnosis were not significantly different between either PI and PI/SD probands. The mean age between all groups was assessed and did not significantly differ ( $P=.756$ ). The mean age of 63 men ( $44.7 \pm 1.9$ ) and the mean age of 48 females ( $46.8 \pm 1.9$ ) were not statistically different ( $P=.46$ ). For this investigation, in 16 controls (CS), sexual selection included 63 percent females and 37 percent males; in 34 PI probands, 62 percent females and 38 percent males; and in the 61 PI/SD group, 52 percent females and 48 percent males ( $P=.835$ ). Pearson Chi Square revealed a non-significant difference between groups in terms of all diagnoses ( $P=.117$ ) and the 3 main diagnoses ( $P=.46$ ).

In order to further characterize the severity of substance use disorder, we subdivided 61 PI subjects into 19 alcohol abusers [(31%) 305.00 (AA)], 23 alcohol dependent [(38%) 303.90 (AD)], and 19 (31%) cocaine dependence and abuse using subjects (COKE) categorized as 304.20 cocaine dependence [(16%) 304.20 ( $N=10$ )] and cocaine abuse [(15%) 305.60 ( $N=9$ )]. Age, gender, and diagnosis demographic data of these subgroups are illustrated in Table 1.

## Selection Criteria and

## Assessment Instruments

The following selection criteria and assessment instruments were utilized: (1) DSM IV Axis I diagnoses of a psychiatric disease; (2) clear predominance of one symptom type; (3) absence of neurological symptoms as identified by history, physical examination, as well as, in some cases, neurological examination at the time of the brain map study; (4) medication-free for at least 24-72 hours prior to the brain map; (5) drug-free for at least one month prior to the brain map; (6) when necessary we utilized the Millon Clinical Multiaxial Inventory II to clarify the diagnosis; (7) Holmes Rahe Life Events Scale;<sup>62</sup> (8) at least one initial psychiatric (modified structured) clinical interview drawn from DSM IV and a comprehensive psychiatric history, a modified Brief Psychiatric Rating Scale and a modified Hamilton Depression and Anxiety Scale, and a blind confirming follow-up evaluation and/or review by a

**Table 1**

Demographic and diagnostic characteristics of controls, psychiatrically-ill patients,  
and categorized substance use disorders with evidence of comorbid psychiatric problems

Group	Number	Age $\pm$ S.E. <sup>1</sup>	Sex <sup>2</sup>		Dysthymia <sup>3,4</sup> %	GAD <sup>5</sup> %	Unipolar %	Bipolar %	ADHD <sup>6</sup> %	Schizophrenia %
			M (%)	F (%)						
Control	16	48.9 $\pm$ 3.9	37.5	62.5	0	0	0	0	0	0
Psychiatric PI	34	45.5 $\pm$ 2.4	38.2	61.8	35.3	2.9	35.3	2.9	20.6	2.9
AA (a)	19	46.1 $\pm$ 3.2	47.4	52.6	52.7	5.3	10.5	0	21.1	10.5
AD (b)	23	47.1 $\pm$ 2.8	52.2	47.8	43.5	0	17.4	0	34.8	4.3
COKE (c)	19	42.5 $\pm$ 3.9	42.1	57.9	26.3	0	26.3	21.1	21.1	5.3
AD + COKE	42	45.0 $\pm$ 3.3	47.6	52.4	35.7	0	21.4	9.5	28.6	4.8
PI/SD (d)	61	45.3 $\pm$ 3.3	47.5	52.5	41.0	1.6	18.0	6.6	26.2	6.6

a. AA = Alcohol Abuse

b. AD = Alcohol Dependence

c. COKE = Cocaine Abuse and Dependence

d. PI/SD = Psychiatrically-ill Substance Use Disorder consists of a,b,c

1. Analysis of Variance  $P = .756$

2. Pearson Chi Square  $P = .835$

3. All diagnoses Pearson Chi Square  $P = .117$

4. Psychiatric diagnoses Pearson Chi Square  $P = .46$

5. GAD = Generalized Anxiety Disorder

6. ADHD = Attention Deficit Hyperactivity Disorder NOS

board certified or eligible psychiatrist; (9) in select patients the Minnesota Multiphasic Personality Inventory-2 as well as Neuropsychological Assessment; (10) all subjects also filled out a Medical History and Brain Mapping Assessment Inventory; (11) follow-up consisted of one or more interviews within two to four weeks of initial entry into the study; and (12) medically evaluated as free from neurological disease.

All patients met the minimum DSM IV Axis I criteria of at least one of six psychiatric diagnoses: dysthymia (300.4), generalized anxiety disorder (GAD) (300.02), bipolar I disorder, most recent episode unspecified (296.7), attention deficit hyperactivity disorder (not otherwise specified, 314.9), major depressive disorder (recurrent, 296.3), and schizophrenia (paranoid type, 295.30) (Table I). All subjects were psychiatrically assessed by similar instruments as described above.

Since it is difficult to accurately ascertain lifetime substance use (LSU) disorder, in patients<sup>63,64</sup> in our study we assessed LSU utilizing a number of criteria and instruments (see below) and found the PI and CS groups to be free from any LSU.

To assess alcohol and drug dependency and abuse patterns, each subject received a structured interview to determine the presence/absence of a substance use disorder by a certified drug and alcohol counselor; and a conferring blind psychiatric review by a consulting board certified or board eligible psychiatrist. Clinical exam verified abstinence prior to testing. Utilizing these assessment tools we were able to ascertain early full remission of substance use disorder (DSM IV).

For 111 of the subjects, substance use was assessed according to the following: (1) DSM IV lifetime psychoactive substance use disorder (cocaine abuse, 305.60 and cocaine dependence, 304.20); (2) DSM IV alcohol dependence (303.90) and alcohol abuse (305.00); and (3) utilization of the alcohol and drug use history inventory - an 18-page questionnaire developed by Dr. Ernest Noble at UCLA. Validity of the UCLA questionnaire was further verified by SADQ analysis as observed in previous studies.<sup>65-67</sup> This last procedure assessed for a family history of alcohol/drugs, frequency and quantity of peak psychoactive lifetime use, as well as clinical history of treatment. This quantity-frequency approach was chosen because of evidence that heavy use of alcohol may display significant heritability. This instrument also provided an assessment of drug/alcohol severity use pat-

terns. Selection mandated that the drug use was not active for at least four weeks prior to the brain map, as assessed by history. The patients were assessed for life time use, and came to an outpatient clinic to enhance well being and/or recovery. There was a 100% agreement on drug use history between two independent clinical raters. Additionally, to further categorize each substance use disorder subject, their first drug of choice was assessed. All subjects were part of a catchment study involving DRD2 receptor gene which received IRB approval from the University of Texas Health Science Center at San Antonio and PATH Foundation, and whereby the patient filled out an approved consent form.

### ELECTROPHYSIOLOGICAL METHODS

A total of 111 subjects were analyzed by BEAM® (Nicolet Instruments). A 24-channel EEG recorder was utilized using the standard 10/20 system of electrode placement, plus two earlobe and two supraorbital electrodes, and two EKG electrodes connected to the cervical spine. Our group used electrocap and found no difference between BEAM® with or without electrocap. Electrocap has been used effectively at major centers in epilepsy research.<sup>68-70</sup> Digitized EEG was recorded in monopolar (LR linked ears left over right) and bipolar (LR 3, 4 linked ears left over right) montage for one hour. Digitized EEGs, spectral analysis, and EP (evoked potentials) were stored on an optical disc. Eye, EMG, and EKG monitors were employed throughout the recording. Grass photic stimulation (model PS22C) at .5 hertz was performed. The tracing captured wakefulness and drowsiness. The BEAM® procedure consists of an EEG, eyes open and eyes closed, spectral analysis, Visual Evoked Response (VER) (3 runs of 100 flashes at .5 hertz), Auditory Evoked Response (AER) (3 runs of 100 clicks by earphone), and P300 tests done by standard auditory oddball paradigm of burst tones (1 KHz frequent, 2 KHz rare tone, 85 db SPL [Sound Pressure Level] with analysis of difference between frequent and rare tone, see Table 2).

Interobserver reliability was 100% for topographical changes in EEG in all subjects included in this study. EEG was read by an independent electroencephalographer without knowledge of subject diagnosis and a conferring physician trained in EEG. Encephalographers rated each EEG study, using conventional EEG criteria to assess the degree of cerebral dysrhythmia, including estimated posterior dominant frequency and amount of slow wave activity in the theta

under one factor those variables that are inter-  
to a much smaller set of factors by grouping  
the approach. PCA also reduces large data sets  
components Analysis in PCA.<sup>40,48-52</sup> Like our compos-  
ject by utilizing factor analysis or Principal Com-  
albeit Duffy's group who approached this sub-  
by developing sound and justifiable composites,  
systematically approach statistical assessment  
To our knowledge this is the first attempt to

ize the EPS abnormalities.  
eight subcomposites (Tables 5 and 6) to local-  
nent measurement. EPS was subdivided into  
ing the P300-P2 data as an individual compo-  
basic principal composites (TSA + EPS), retain-  
brain electrophysiological mapping to only two  
der).<sup>24,26,28,30</sup> In our study we thus reduced the  
ic disorder and comorbid substance use disor-  
components in a variety of disease states (pan-  
potentials, and have clinically accessed such  
nents of both spectral analysis and evoked  
have clustered a number of individual compo-  
measures is based on previous studies which  
The rationale to develop these composite

evoked potentials (also by location).  
power, symmetry, coefficient of variations), and  
lated for spectral analysis (eyes open and closed,  
measures within a class of measures, was calcu-  
accomplish this aim, the sum of the abnormal  
number of logical composite measures.<sup>78</sup> To  
occipital, and parietal), we decided to develop a  
sis, and electrode placement (temporal, frontal,  
subcategorized EP abnormalities, spectral analy-  
results from performing 53 separate ANOVAs by  
the high probability of a Type I statistical error that  
"capitalization on chance"). Therefore, to eliminate  
due to chance is high (i.e. Type I statistical error or  
then the probability of finding "significant" values  
If these variables are uncorrected in some way,  
by the number of electrodes used.

Such a number can be estimated by multiplying  
of variables, often in the several thousand range.  
the issue, QEEG studies result in a large number  
statistical tests.<sup>40,74-78</sup> Moreover, to summarize  
stantive QEEG issue has been that of "too many  
Recently, Duffy et al.<sup>40</sup> pointed out that a sub-  
msec per year, increase in P300 after age 18.<sup>72</sup>  
Boulder, Colorado, and an approximate 1.25  
which is a criteria developed by Lexicor Inc,  
mean age of the control group ( $48.9 \pm 3.9$ )  
on an approximate estimate of 300 ms plus  
dichotomized at 350 ms (this value was based  
mal voltage of 10dV<sup>5,7,18</sup>. P300 latency was  
voltage was dichotomized at an established nor-

For statistical analysis, all brain map data  
were classified as abnormal or normal. Specifi-  
cally, EEG was dichotomized as normal or abnor-  
mal; spectral analysis was dichotomized at 2.0  
SD from standardized BEAM® controls; EPS  
were dichotomized at 2.5 SD from BEAM® con-  
trols with recurrence of deficits (at the same  
loci) following three independent test runs; P300

### Statistical Analysis

and occipital regions (see Table 2).  
Similar evaluations were done for frontal, parietal,  
measurements were done for VEP and AEP only.  
both temporal lobes in the same epoch. Such  
defined as one or more abnormalities occurring at  
being evaluated. Bitemporal abnormalities were  
abnormal with each time epoch (25 over 500 ms)  
dard deviations (SD) or more, it was ranked as  
portal lobe electrodes was abnormal at 2.5 stan-  
and F7, T3, T5 (left temporal). If one or more tem-  
lobes were measured at F8, T4, T6 (right temporal)  
Abnormalities of electrophysiology of temporal

### Electrophysiological Localization Data

#### Measurement and Interpretation of

was 51 (see Table 2).  
(beta 2, beta 3, and figure of merit) and EEG,  
meters measured, excluding the artifact files  
to the BEAM system.<sup>38</sup> The total number of para-  
ized and color coded topographically according  
P<sub>2</sub>, N<sub>2</sub> and AEP N<sub>1</sub>, P<sub>1</sub>, N<sub>2</sub> - values were normal-  
read for N (negative peak), P (positive peak),  
VEP was calculated after three runs. VEP was  
16-19.5, and beta 3 20-24. An average AEP and  
3.5, theta 4-7.5, alpha 8-11.5, beta 1 12-15.5, beta 2  
spectral analysis of six bands of hertz: delta 0-  
total brain map analysis which consisted of  
ward.<sup>72</sup> All groups described above underwent  
BEAM II System provided by Frank Duffy at Har-  
a control group data base (n=60) of the Nicolet  
parameters in probands and controls, we utilized  
in order to compare electrophysiological

differential voltage (dV).  
bands. P300 was analyzed at Pz, for time and  
variation were done for spectral analysis in all  
msec, and power, symmetry, and coefficient of  
VEP and AEP were analyzed at 20 msec, for 500  
Evoked Potentials (EP). Specifically, both the  
interpeak latencies were all analyzed in the  
ond epochs of EEG. Amplitude latencies and  
analysis was analyzed after ten or more two sec-  
dysrhythmia score to each EEG study. Spectral  
criteria<sup>77</sup>, which was used to assign an overall  
amount). This is the Mayo Clinic classification  
1=minimal amount, 2=moderate amount, 3=large  
and delta frequency ranges (scored as 0=none,

**Table 2**  
Brain electrical activity mapping parameters measured and composites

EEG and Spectral Analysis		Evoked Potentials	Evoked Potentials Locations	P300 Cognitive Evoked Potentials	Composites And Subcomposites
EEG		VER	AERF	VPZ	TBA
ECLD	EOPD	AER	VERF	PZT	TSA
ECLT	EOPT	VERS	AERBIF		EPS
ECLA	EOPA	AERS	VERBIF		EPS-L
ECLB	EOPB		AERT		AVBIF
ECLSD	EOPSD		VERT		AVBIFA
ECLST	EOPST		AERBIT		AVBIT
			VERBIT		
ECLSA	EOPSA		AERP		AVBITA
ECLSB	EOPSB		VERP		AVBIP
ECLDCV	EOPDCV		AERBIP		AVBIPA
ECLTCV	EOPTCV		VERBIP		AVBIO
ECLACV	EOPACV		AERO		AVBIOA
ECLBCV	EOPBCV		VERO		
			AERBIO		
			VERBIO		

## DEFINITION OF PARAMETERS:

EEG: Electroencephalograph  
 ECL Eyes closed  
 D Delta  
 T Theta  
 A Alpha  
 B Beta  
 S Symmetry  
 CV Coefficient of variation  
 EOP Eyes opened  
 VER Visual evoked response  
 AER Auditory evoked response  
 dV Differential voltage of P300  
 PZ Parietal Central Electrode  
 T Time

## DEFINITION OF COMPOSITES:

TBA Total Brain Mapping Abnormalities  
 TSA Total Spectral Abnormalities  
 EPS AER, AERS, VER, VERS Evoked Potential  
 EPS-L All EPS abnormalities by location  
 AERF AER Frontal  
 VERF VER Frontal  
 AERBIF AER Bifrontal  
 VERBIF VER Bifrontal  
 AERT AER Temporal  
 VERT VER Temporal  
 AERBIT AER Bitemporal  
 VERBIT VER Bitemporal  
 AERP AER Parietal  
 VERP VER Parietal  
 AERBIP AER Biparietal  
 VERBIP VER Biparietal  
 AERO AER Occipital  
 VERO VER Occipital  
 AERBIO AER+VER Bioccipital  
 VERBIO VER Bioccipital  
 AVBIF AER+VER Bifrontal  
 AVBIFA AER+VER All Frontal  
 (AERF+VERF+AERBIF+VERBIF)  
 AVBIT AER+VER Bitemporal  
 AVBITA AER+VER All Temporal Sites  
 (AERBIT+VERBIT+AERT+VERT)  
 AVBIP AER+VER Biparietal  
 AVBIPA AER+VER All Parietal  
 (AERP+VERP+AERBIP+VERBIP)  
 AVBIO AER+VER Bioccipital  
 AVBIOA AER+VER All Occipital

**Table 3**

Brain map comparisons between controls and depressed  
psychiatrically-ill patients with and without comorbid substance use disorder<sup>1</sup>

Brain Map Composite	MANOVA P value <sup>2</sup>	ANOVA P value	Weighted-Linear Trend P Value	Paired comparison of Means-Duncan Range Range Test (P < .05) <sup>3</sup>
TBA	0.005	NA	0.001	NA
TSA	0.008	0.038	0.0113	CS, PI < PI/SD
EPS	0.004	0.0023	0.0022	CS < PI, PI/SD
VPZ	0.045	0.0447	0.0182	CS < PI/SD
PZT	0.288	0.312	0.346	NA

1. The total sample size for this study was 39 probands which was subdivided into 16 controls, 12 depressed psychiatrically-ill patients without co-morbid substance use disorder and 11 depressed psychiatrically-ill patients with co-morbid substance use disorder.
2. VPZ and PZT groups N=32 therefore MANOVA was done on 32 probands.
3. Control group = CS/ Psychiatrically-ill without comorbid substance use disorder = PI, Psychiatrically-ill with comorbid substance use disorder = PI/SD.

correlated.<sup>40, 60-62</sup> Moreover, in order to further reduce or even avoid false positives in clinical QEEG, it becomes not only necessary but expedient to repeat all study conditions multiple times and retain as clinically relevant only those that show consistency across all trials.<sup>40, 79</sup> We are the first to use such composite scores in the subsequent statistical analysis, but the same pattern was described by Duffy. It is our contention that by utilizing both composite measures and MANOVA, the "too many statistical tests" criticism has been adequately answered. However in an attempt to further reduce the Type I error possibility, we decided to utilize the multivariate analysis of variance (MANOVA) approach which reduces the number of tests measured (TBA-Total Brain Abnormalities-all BEAM parameters). This approach provided between-group comparisons for those composite EEG measures, displaying univariate analysis or variance (ANOVA). For statistical calculations we employed the SPSS computer program (Statistical Package for the Social Sciences, SPSS, Inc., version 4.0). Weighted linear trends were examined in the ANOVAs. A linear increase in abnormal values was predicted going from control to PI to PI/SD (alcohol abuse and alcohol dependence and then cocaine abuse and dependence).

We further employed a Duncan Range test for paired comparison of means. The alpha probability level was set at .05 for significance.

## RESULTS

Table 3 shows the mean difference, MANOVAs, weighted linear trends, and paired comparisons of the means in a number of composite param-

eters including TBA, TSA, EPS, as well two independent P300 measures VPZ and PZT. The Table includes all parameters analyzed and significance of the ANOVAs was not adjusted for the number of tests that were performed. Comparison within these composite groups and between assessed controls, PI and PI/SD groups revealed a number of significant differences in terms of electrophysiological abnormalities as measured by brain electroactivity mapping.

In terms of TBA, utilizing the MANOVA approach, we found that with regard to this composite (see Table 2) both PI and PI/SD groups had more total brain electrophysiological abnormalities relative to CS (P=.017). A linear contrast revealed increasing TBA's with increasing substance use disorder (P=.003). MANOVA P values were TSA .008, EPS .004, VPZ .045, PZT .288, respectively. The MANOVA had an N=89 due to missing P300 values, therefore we preceded to the ANOVAs.

In terms of the univariate ANOVAs we found a number of interesting and significant findings. We found that with regards to the composite TSA (see Table 2), both the PI and PI/SD groups had more overall abnormalities in brain topography relative to CS. In the TSA composite we found an ANOVA of P=.038.

Moreover, utilizing a weighted linear trend (P=.0113) there were increasing spectral abnormalities with increased substance use disorder. The Duncan Range test further revealed that the PI/SD group had significantly greater abnormalities than the CS group. (see Table 3).

Similar results were found for the event-related potential composite we termed EPS (see Table



Table 4

Brain map comparisons between controls and depressed  
psychiatrically-ill patients with and without comorbid substance use disorder<sup>1</sup>

Brain Map Composite	MANOVA P value <sup>2</sup>	ANOVA P value	Weighted-Linear Trend P Value	Paired comparison of Mearis-Duncan Range Range Test (P < .05) <sup>3</sup>
TBA	0.043	NA	0.006	NA
TSA	0.065	0.0169	0.0059	CS, PI < PI/SD
EPS	0.001	0.0002	0.0001	CS < PI, PI/SD
VPZ	0.090	0.0904	0.034	NA
PZT	0.288	0.288	0.26	NA

1. The total sample size for this study was 39 probands which was subdivided into 16 controls, 12 depressed psychiatrically-ill patients without co-morbid substance use disorder and 11 depressed psychiatrically-ill patients with co-morbid substance use disorder.
2. VPZ and PZT groups N=32 therefore MANOVA was done on 32 probands.
3. Control group = CS, Psychiatrically-ill without comorbid substance use disorder = PI, Psychiatrically-ill with comorbid substance use disorder = PI/SD.

2). In this regard, both the PI and PI/SD groups had more event-related potential abnormalities relative to CS. We found that in the EPS composite the resultant ANOVA was significant at ( $P=.0023$ ). A weighted linear trend ( $P=.0022$ ) showed increasing event-related potential abnormalities with increased substance use disorder. Additionally, the Duncan Range test revealed that both the PI and PI/SD groups had significantly greater abnormalities than the CS group.

With regard to the P300 data in particular VPZ (see Table 2), we found a significant ANOVA ( $P=.0447$ ). A weighted linear trend also revealed significance ( $P=.0182$ ), supporting increased abnormalities with increasing substance use disorder. A Duncan Range test further revealed that the PI/SD group had a significantly greater number of abnormalities than the CS group (see Table 3). In contrast, no significant ANOVA was found with the PZT measurement (see Table 3).

In order to further characterize the data, we decided to subdivide the PI and PI/SD groups into only those patients diagnosed with major depressive illness. Table 4 shows statistical comparisons of the means in 16 CS, 12 PI and 11 PI/SD subjects.

In the selected depressed group, we found that with regard to the TBA composite, utilizing the MANOVA approach, both PI and PI/SD groups had more total brain electrophysiological abnormalities relative to CS ( $P<.043$ ). A linear contrast revealed increasing TBAs with increasing substance use disorder ( $P<.006$ ). MANOVA P values reveal TSA .065, EPS .001, VPZ .09, PZT .288, respectively. With regard to the P300 data

set MANOVA analysis resulted in a  $N=32$ . Loss of a measure's significant effect in the depressed subjects is due to smaller sample sizes, not to any reduction in group mean differences. In terms of spectral analysis, we found that in the depressed population, with regard to the composite TSA, both the PI and PI/SD groups had more overall abnormalities in brain topography relative to CS. In the TSA composite we found an ANOVA of  $P=.0169$ . Moreover, utilizing a weighted linear trend ( $P=.0059$ ) there were increasing spectral abnormalities with increased substance use disorder. The Duncan Range test revealed that the PI/SD group had significantly greater abnormalities than the PI group and CS (by weighted linear trend only).

As with the combined groups in the selected depressed subjects, groups were found for the event-related potential composite, EPS. Both the PI and PI/SD groups had more event-related potential abnormalities relative to CS. We found that in the EPS-composite the resultant ANOVA was significant at  $P=.0002$ . The weighted linear trend showed once again, as with the TSA composite, increasing abnormalities with increased substance use disorder ( $P=.0001$ ). However the Duncan Range test revealed that unlike the TSA composite there was no significant difference between the PI and PI/SD groups in terms of number of abnormalities.

With regard to the P300 data, in the depressed group, specifically VPZ (see Table 2), we found no significant ANOVA at the .05 level ( $P=.0904$ ). However, a weighted linear trend did reveal significance ( $P=.034$ ), supporting increased abnor-

Table 5

Brain map comparisons combined with controls and  
psychiatrically-ill patients with and without comorbid substance use disorder.<sup>1</sup>

Brain Map Composite	MANOVA P value	ANOVA P value	Weighted-Linear Trend P value	Paired Comparison of Means-Duncan Range Range Test (P < .05) <sup>2</sup>
EPS-L	0.007	NA	0.012	
AVBIF	0.043	0.0426	0.0153	CS < PI/SD
AVBIFA	0.011	0.0110	0.0050	CS, PI < PI/SD
AVBIT	0.003	0.009	0.0022	CS < PI/SD
AVBITA	0.001	0.005	0.0008	CS < PI, PI/SD
AVBIP	0.222	0.2218	0.1548	NA
AVBIPA	0.097	0.0969	0.0505	NA
AVBIO	0.945	0.9454	0.6376	NA
AVBIOA	0.980	0.9797	0.8797	NA

1. The total sample size for this study was 111 probands which was subdivided into 16 controls, 34 psychiatrically-ill patients without comorbid substance use disorder and 61 psychiatrically-ill patients with comorbid substance use disorder.
2. Control group = CS; Psychiatrically-ill without comorbid substance use disorder = PI, Psychiatrically-ill with comorbid substance use disorder = PI/SD.

malities with increasing substance use disorder. In contrast, no significant ANOVA was found with the PZT measurement (see Table 3).

We decided therefore, to systematically evaluate the location of evoked potential abnormalities in AER and VER files.

In terms of EPS-L (Table 5), utilizing the MANOVA approach, we found that with regard to this composite (see Table 2 and Table 5) both PI and PI/SD groups had more total brain electrophysiological abnormalities relative to CS ( $P=.025$ ). A linear contrast test revealed increasing abnormalities with increasing substance use disorder ( $P=.036$ ).

With reference to the composite trend AVBIF (see Table 5), an ANOVA revealed that both the PI and PI/SD groups had more bifrontal abnormalities in the event-related potential file relative to CS. Thus, we found an ANOVA of  $P=.0426$ . Moreover, a weighted linear trend test showed increasing frontal lobe abnormalities with increasing substance use disorder ( $P=.0153$ ). Furthermore the Duncan Range test revealed that the PI/SD as expected through a literature review<sup>63</sup>, had significantly greater abnormalities than the CS group. Similar results were obtained with all frontal abnormalities AVBIFA (see Table 5), whereby an ANOVA was significant at the  $P=.0110$  level with a weighted linear trend at a  $P=.005$  level. The Duncan Range test also revealed that both PI and PI/SD groups had significantly more abnormalities in the event-related

potential file relative to CS (see Table 5).

Furthermore, with regard to composite AVBIT (see Table 2), an ANOVA revealed that both the PI and PI/SD groups had more bitemporal abnormalities in the event-related potential file relative to CS. Thus, we found an ANOVA of  $P=.009$ . Moreover, utilizing a weighted linear trend ( $P=.0022$ ) the results showed that increasing EP abnormalities in both temporal lobes increased with substance use disorder. Additionally the Duncan Range test showed that the PI/SD group had more abnormalities than controls but did not differ significantly from the PI group (see Table 5).

Moreover, when we evaluated the AVBITA composite (see Table 2), a similar result occurred. An ANOVA revealed that both the PI and PI/SD groups had more total temporal abnormalities in the EP file relative to CS ( $P=.0026$ ). A weighted linear trend showed increasing abnormalities in the bitemporal lobes with increasing substance use disorder ( $P=.0008$ ). When the Duncan Range test was applied we found that the PI/SD and PI group was worse than CS, but PI and PI/SD groups were not significantly different.

When we calculated similar statistics with regard to the EP composite AVBIP, AVBIPA, AVBIO and AVBIOA (see Table 5), no significant differences were observed utilizing ANOVA (see P values in Table 5) at the .05 level.

Table 6 shows the MANOVA for EPS-L in depressed patients only whereby  $P=.00026$  with a weighted linear trend of  $P=.000067$ . Moreover,

Table 6

Brain map comparisons between controls and depressed  
psychiatrically-ill patients with and without comorbid substance use disorder<sup>1</sup>

Brain Map Composite	MANOVA P value	ANOVA P value	Weighted-Linear Trend P value	Paired Comparison of Means-Duncan Range Test (P < .05) <sup>2</sup>
EPS-L	0.00026	NA	0.000067	NA
AVBIF	0.012	0.0116	0.0054	CS, PI < PI/SD
AVBIFA	0.012	0.0116	0.0065	CS, PI < PI/SD
AVBIT	0.00002	0.00002	0.000004	CS < PI < PI/SD
AVBITA	0.000015	0.000015	0.000003	CS < PI < PI/SD
AVBIP	0.154	0.1542	0.1454	NA
AVBIPA	0.077	0.0770	0.0645	NA
AVBIO	0.393	0.3935	0.417	NA
AVBIOA	0.725	0.7250	0.5221	NA

1. The total sample size for this study was 111 probands which was subdivided into 16 controls, 34 psychiatrically-ill patients without comorbid substance use disorder and 61 psychiatrically-ill patients with comorbid substance use disorder.
2. Control group = CS; Psychiatrically-ill without comorbid substance use disorder = PI, Psychiatrically-ill with comorbid substance use disorder = PI/SD.

in these selected depressed subjects, (Table 6) similar results were observed with regard to the AVBIF composite. An ANOVA revealed that the PI/SD groups had more EP abnormalities in the bifrontal lobes relative to PI and CS groups ( $P=.0116$ ). When we compared using Duncan's differences between the groups, we found that the PI/SD group had significantly more abnormalities than either PI or CS groups. A weighted linear trend test revealed a highly significant P value at .0054 (see Table 6).

With regard to the AVBIFA composite, similar results were obtained. An ANOVA revealed that both the PI and PI/SD groups had more EP abnormalities in all frontal lobe abnormalities relative to CS ( $P=.0116$ ). Moreover, when we compared the difference between the groups using Duncan's Range test, we found that the PI/SD group had significantly more abnormalities than either PI or CS groups. A weighted linear trend revealed a significant P value at .0065 (see Table 6).

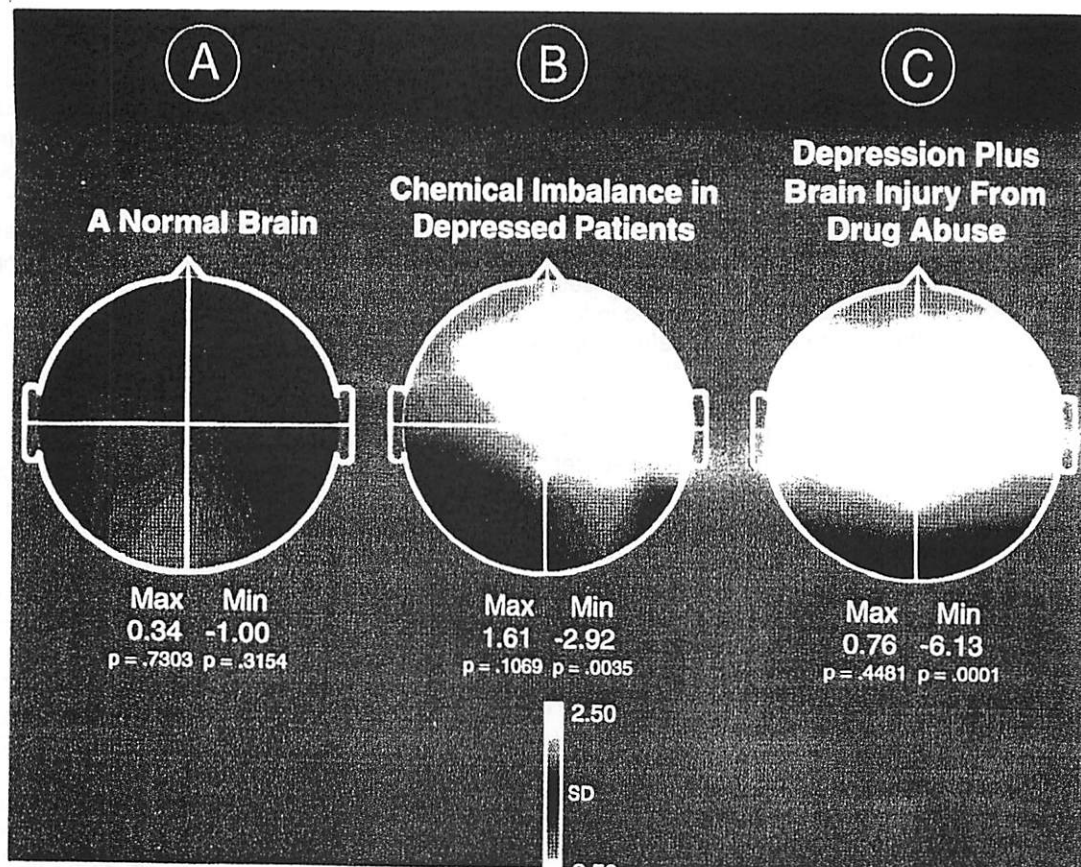
When we looked at the AVBIT composite in the depressed patients, we also found a significant difference in terms of EP abnormalities ( $P=.00002$ ) by ANOVA. In this regard, we also found that the PI/SD group had significantly more bitemporal EP abnormalities than both the PI and CS groups and PI more than CS. Therefore in these select depressed patients, a weighted linear trend analysis revealed a significant P value = .000004 (see Table 6).

In selected depressed subjects, similar results

were observed with regard to the AVBITA composite. An ANOVA revealed that both the PI and PI/SD groups had more EP abnormalities in all temporal lobes relative to CS ( $P=.000015$ ). When we compared differences in the Duncan Range test between the groups, we found that the PI/SD and PI group had significantly more abnormalities than the CS groups and PI/SD more than PI. A weighted linear trend revealed a highly significant P value at .000003 (see Table 6).

The EPS data, especially with regard to the AVBIT composite, represent the strongest finding in the entire data set, and we therefore decided to provide a pictorial with regard to this profound finding (Figure 1A, B, C).

Figure 1A is a significant probability topographic map (SPM) of the VER in a typical normal subject. On visual inspection, a homogenous blue-black, electrically stable brain electrical activity map is seen. Standard deviation (SD) maximum (0.34) and minimum (-1.00) are shown here as SPM, and our control group is not significantly different from the standardized BEAM® controls. Figure 1B shows a characteristic brain electrical activity map of the VER in a single psychiatrically-ill patient with unipolar depression, with a right temporal excess negativity to 2.90 SD as shown by a bright white-blue. The right temporal abnormality exhibited by the light white-blue area is typical of individuals with depression, i.e. mood swings, palpitations, anxiety, and stress, with or without substance use disorder. Figure 1C shows a character-



**Figure 1A:** is a significant probability topographic map (SPM) of the VER in a typical normal subject. On visual inspection, a homogenous blueblack, electrically stable brain electrical activity map is seen. Standard deviation (SD) maximum (0.34) and minimum (-1.00) are shown here as SPM, and our control group is not significantly different from the standardized BEAM® controls.

**Figure 1B:** shows a characteristic brain electrical activity map of the VER in a single psychiatrically-ill patient with unipolar depression, with a right frontal temporal excess negativity to 2.92 SD as shown by a bright white-blue. The right frontal temporal abnormality exhibited by the light white-blue area is typical of individuals with depression, ie., mood swings, palpitations, anxiety, and stress, with or without substance use disorder.

**Figure 1C:** shows a characteristic brain electrical activity map of the VER in a substance use disorder patient with unipolar depression, with a left and right frontal temporal excess negative to 6.13 SD as shown by a bright white-blue. This map may also be a characteristic of patients with a history of substance use disorder with or without depression and violence.

istic brain electrical activity map of the VER in a substance use disorder patient with unipolar depression, with a left and right temporal excess negative to 6.13 SD as shown by a bright white-blue. This map may also be a characteristic of patients with a history of substance use disorder with or without depression and violence.<sup>84</sup>

When we carried out similar statistical tests with regard to the EP composite AVBIP, AVBIPA,

AVBIO, and AVBIOA (see Table 2) no significant differences were observed utilizing ANOVA (see P values in Table 6).

## DISCUSSION

This paper highlights the spectrum of brain electrical activity mapping abnormalities associated with substance use disorder, predominantly cocaine and alcohol, as well as psychiatric

patients with diagnoses of dysthymia (300.4), generalized anxiety disorder (GAD)(300.02), bipolar I disorder (most recent episode unspecified, 296.7), attention deficit hyperactivity disorder (not otherwise specified, 314.9), major depressive disorder (recurrent, 296.3), and schizophrenia (paranoid type, 295.30). Supportive of targeting these psychiatric diagnoses, it is noteworthy that recent papers argue in favor of comorbidity of both attention deficit disorder, major depression,<sup>85,86</sup> and other psychiatric diagnoses<sup>87</sup> with substance use disorder. Depression may also be a premorbid factor in substance use disorder<sup>88</sup> and in attention deficit disorder.<sup>89,90</sup> This is the first time that a study has attempted to evaluate the effect or impact that comorbid substance use disorder may have on patients with psychiatric disease with regard to electrophysiological parameters.

This work confirms previous published reports that indeed there are multiple abnormalities in brain map components of substance use disorder populations.<sup>20-37</sup> In the present study, relative to CS, both the PI and PI/SD groups had more total brain abnormalities as assessed by brain topography. Moreover, utilizing the Duncan Range test, increasing abnormalities were observed in the PI/SD groups compared to CS in spectral analysis.

It is noteworthy that total brain map abnormalities have been further characterized by levels of cerebral dysrhythmia which may represent degrees of kindling. In this regard, levels of cerebral dysrhythmia have been characterized by Frank Duffy, M.D. (personal communication)<sup>72</sup> and the Mayo Clinic Rating System,<sup>73</sup> to include the following categories: (1) seizures, (2) EEG dysrhythmia, (3) other spectral analysis abnormalities graded 1-3, (4) coefficient of variation - abnormal background rhythm, and (5) evoked potential abnormalities. Of those five categories, the most sensitive parameter is evoked potential.<sup>52</sup>

Findings from the present study reveal no significant differences with regard to non-computerized EEG abnormalities between all groups investigated. We did find preliminarily, that the predominant effect on theta (spectral analysis) in the PI and PI/SD groups is not surprising since it has been reported that theta abnormalities occur concomitantly with alpha slowing in substance use disorder<sup>25,26,31</sup> and psychiatric diseased<sup>1,8,91,92</sup> populations. Concerning cerebral dysrhythmia levels preliminarily, we also found that only in the cocaine population significant

abnormalities occurred in ECLCV and EOPBCV for the coefficient variation files. Further support for enhanced cerebral dysrhythmia is derived from our findings that evoked potential abnormalities are greater and more abundant in the substance use disorder population, as are the coefficient of variation abnormalities, compared to the CS group.

P300 abnormalities are well documented but are not specific to drug abuse as once thought. They are also common in ADD,<sup>1,27</sup> schizophrenia,<sup>5</sup> delirium and dementia,<sup>91,92</sup> obesity,<sup>93</sup> and other psychiatric disorders.<sup>7,13,32,34</sup> Our findings of a significant decrease of P300 (VPZ) voltage in the PI/SD group compared to CS is in full agreement with the literature.<sup>2,30,31,34,36</sup>

Since we found differences in the evoked potential data when we compared PI and PI/SD with CS groups, especially in the major depressive disorder group, we decided to further characterize these deficits by location. All temporal parameters were abnormal when PI/SD were compared to CS in the total psychiatric population (see Table 5).

Table 6 (depressed group only) best supports Figures 1A, B, and C since we found increased temporal lobe evoked potential abnormalities in both PI and PI/SD groups relative to CS in the AVBITA composite. It is particularly important that major depression when associated with substance use disorder produces more organic abnormalities for it also is associated with an extremely high rate of suicide.<sup>94</sup> In the depressed patient group, total bitemporal abnormalities (AVBIT) are significantly greater in the PI/SD group than in the PI group.

These results were also found by others<sup>28</sup> where substance use disorder subjects had abnormalities in both temporal regions, whereas matched panic disorder controls had the same abnormalities in only one temporal region.

The bitemporal predominance of evoked potential abnormalities found in substance use disorder subjects may have further significance in that violent drug abusers may also have a predominance of similar evoked potential abnormalities.<sup>84</sup> Furthermore, substance use disorders like premorbid depression may premorbidly predispose probands to subsequent Alzheimer's encephalopathy, concomitant attention deficit disorder, and other psychiatric diseases which may originate in the temporal lobes.<sup>85-87</sup> Brain mapping temporal lobe abnormalities correlate to hypometabolism on PET scan, which is similar



to interictal temporal lobe seizure disorder patients who also have hypometabolism.<sup>98</sup> Our findings support the hypothesis that severe substance use disorder promotes kindling. Moreover, cocaine is known to induce a kindling or electrophysiological instability.<sup>46,48</sup> This may in part induce aberrant evoked potential and spectral analysis abnormalities, as we observed in our cocaine population as well as others. Similarly, ethanol also temporarily corrects evoked potential abnormalities but also induces a kindling response.<sup>47,99</sup> Confirming the potential usefulness of the current findings, Gerez and Tello<sup>52</sup> reported that spectral analysis and evoked potential changes were better predictors of response to anticonvulsants than the presence and/or identification of epileptiform activity through EEG. In light of all the evoked potential abnormalities identified in both psychiatric and substance use disorder groups in our study, it is not surprising that anticonvulsants have widespread clinical utility.<sup>44,46,53,54,100</sup> Furthermore, other therapeutic interventions have also been shown to improve evoked potential abnormalities as well as spectral analysis, such as cholinergics,<sup>101,102</sup> cholinesterase inhibitors,<sup>102-104</sup> dopaminergic and serotonergic agents,<sup>105,106</sup> stimulants,<sup>15,16,19,103</sup> amino acids,<sup>105-107</sup> trace elements,<sup>108,109</sup> diet (i.e., low refined carbohydrates),<sup>105,108,110</sup> cranial electrical stimulation,<sup>35</sup> biofeedback,<sup>111</sup> and finally, a variety of pharmacotherapeutic components.<sup>112-115</sup> Correction of evoked potential abnormalities has been correlated with recovery from psychiatric disease and drug use.<sup>25,34,100,116</sup>

In addition, we found increased abnormalities in the EPS composite in the frontal lobe (but not the occipital and parietal lobes) of the PI/SD groups relative to CS in our total population as well as the select depressive group. This finding was not unexpected since it is known that frontal lobe dysfunction occurs in psychiatric patients (i.e. depression,<sup>83</sup> dysthymia,<sup>117</sup> schizophrenia,<sup>118</sup> and attention deficit disorder,<sup>119,120</sup> as well as in substance use disorder.<sup>25,30</sup>

Our findings should be interpreted with caution at this time because assessment of substance use disorders as well as other psychiatric medication in terms of recent drug use was not validated since tissue/fluid drug analysis of each patient was not performed. However, it is noteworthy that it is our clinical assessment that, as mentioned earlier, these patients reported no substance use at least 4 weeks prior to entry into the study. In terms of psychiatric medication,

approximately 10-20% of these subjects in each group had been prescribed medication in the last month prior to entering the study but were asked to terminate this use at least 24 to 72 hours prior to the brain map. Moreover, the impact if any due to medication is frequently adjusted by an experienced encephalographer. Nevertheless, patients were motivated not to use drugs, and electrophysiological abnormalities are only partially state related.<sup>34,99</sup> In fact, Blanchey et al<sup>9</sup> found that recovering substance abusers still had a low P300 even after substance use was discontinued. The P300 activity only partially recovers and also represents a genetic characteristic antedating substance use leading to cocaine or heroin abuse similar to that observed in alcoholics.<sup>9</sup>

### Implications for Prevention

The most important contribution of this paper is the finding that there are identifiable, increased electrophysiological disturbances (particularly spectral analysis, i.e., theta, and evoked potentials, i.e., frontal, temporal and especially bimodal) in substance use disorder subjects when compared to a non-substance use disorder group having similar psychiatric problems. In preliminary research increased electrophysiological disturbance in the EPS file, is associated with severity of substance use disorder (alcohol dependence is worse than alcohol abuse and cocaine has a higher abuse liability - more adverse medical and social effects), which seems to parallel the reported association of the dopamine D2 receptor (dopamine being an important substrate or reward) gene variants in severity of alcoholism,<sup>65-67,121-125</sup> substance use disorder,<sup>126-129</sup> and other psychiatric disorders (Tourette's,<sup>130</sup> ADD,<sup>131</sup> post-traumatic stress disorder,<sup>130</sup> obesity,<sup>131</sup>) as well as receptor expression.<sup>132,133</sup>

This genetic evidence, along with other studies of electrophysiological disturbances in children of alcoholics,<sup>30,31,36,66-67,134,135</sup> suggests a premorbid existence of greater electrophysiological disturbances in the cocaine and alcohol abuse/dependence group in a psychiatrically-ill population. However, it has been reported that substance use disorder exacerbates brain mapping parameters,<sup>27,28,34,99</sup> and when abstinence occurs, there appears to be persistence of some drug-induced brain electrophysiological damage in most cases.<sup>25,27,28,34,99</sup> It would appear that both the genotype and phenotype of substance use disorders provide useful information for treatment.<sup>136</sup> While it is true that this study is ill-

equipped to provide definitive answers with regard to the gene-environment issue, other work in our laboratory is underway which will address this issue by evaluating the link between DRD2 gene variants, brain electrical activity mapping and "Reward Deficiency Syndromes" in a similar population.

Finally, we theorize that comorbid substance use disorder in psychiatric probands significantly exacerbates a potential premorbid state and strongly suggests a gene-environment interaction.<sup>137-139</sup> The self-medication, or specifically cocaine and alcohol abuse/dependence (substance use disorder), used to relieve these electrophysiological disturbances, unfortunately results in worsening of brain dysfunction, especially in the bitemporal lobes of the brain, especially in depressed patients, and the induction of possible permanent kindling of the brain as evidenced (fronto-temporal) by increased EPS and spectral analysis abnormalities in PI/SD. In this regard, the kindling model proposes that repeated environmental stimuli such as substance use disorder, lead to progressively greater neural response particularly in the frontal and temporal regions, which increase brain excitability and lead to long lasting psychiatric disease.

In terms of the relevance of this study to substance use disorder among teenagers, it is tempting to speculate, that since cocaine and alcohol abuse/dependence clearly exacerbates electrophysiological brain abnormalities in psychiatrically-ill patients (especially in depressed probands), potentially through a neurotoxic mechanism<sup>140,141</sup> young people provided with this information should increase their perceived risks of dependence on alcohol, cocaine, and probably other psychoactive chemicals,<sup>142,143</sup> thereby

reducing potential lifetime substance use disorder. Our work suggests that treatment may need to take into account genetic,<sup>144-146</sup> psychiatric,<sup>147</sup> substance use,<sup>148</sup> metabolic<sup>149</sup> and electrophysiological<sup>150-153</sup> comorbid data.

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## REFERENCES

1. Braverman ER. Brain mapping: a short guide to interpretation, philosophy and future. *J Orthomolecular Med* 1990; 5:4.
2. Daniels EK, Shenton ME, Holzman PS, et al. Patterns of thought disorder associated with right cortical damage, schizophrenia, and mania. *Amer J Psychiatry* 1988; 145(8):944-9.
3. Stoudemire A, Nelson A, Houpt JL. Interictal schizophrenia-like psychoses in temporal lobe epilepsy (Review). *Psychosomatics* 1983; 24(4):331-3, 337-9.
4. Braverman ER. Brain electrical activity mapping in treatment resistant schizophrenics. *J Orthomole Med* 1990; 5(1):46-48.
5. Morstyn R, Duffy FH, McCarley RW. Altered P300 topography in schizophrenia. *Arch Gen Psychiatry* 1983; 40(7):729-34.
6. Karson CN, Coppola R, Morihisa JM, Weinberger DR. Computed electroencephalographic activity mapping in schizophrenia: the resting state reconsidered. *Arch Gen Psychiatry* 1987; 44(6):514-7.
7. Neshige R, Kuroda Y, Kakigi R, et al. Event-related brain potentials as indicators of visual recognition and detection of criminals by their use. *Forensic Sci Int* 1991; 51(1):95-103.
8. Blanchey MH, Buydens-Blanchey L, Horvath TB. Event-related potentials in substance abusers after long-term abstinence. *Biol Psychiatry* 1992; 31:61A-252A.
9. Vasile RG, Duffy FH, McAnulty G, et al. Abnormal flash visual evoked response in melancholia: a replication study. *Biol Psychiatry* 1992; 31(4):325-36.
10. Duffy FH, Albert MS, McAnulty G. Brain electrical activity in patients with presenile and senile dementia of the Alzheimer type. *Ann Neurol* 1984; 16(4):439-48.
11. de Toledo-Morrell L, Evers S, Hoepfner TJ, et al. A 'stress' test for memory dysfunction: electrophysiological manifestations of early Alzheimer's disease. *Arch Neurol* 1991; 48(6):605-9.
12. Bernad PG. EEG and pesticides (Review). *Clin Electroencephalogr* 1989; 20(2):IX-X.
13. Morrow LA, Steinhauer SR, Hodgson MJ. Delay in P300 latency in patients with organic solvent exposure. *Arch Neurol* 1992; 49(3):315-20.
14. Knoll O, et al. EEG indicates aluminum load in long term hemodialysis patients. *Trace Elements Med* 1984; 1:54-58.
15. Kugler CF, Lottéer E, Petter J, et al. Visual event-related P300 potentials in early portosystemic encephalopathy. *Gastroenterology* 1992; 103(1):302-10.
16. Messenheimer JA, Robertson KR, Wilkins JW, et al. Event-related potentials in human immunodeficiency virus infection. *Arch Neurol* 1992; 49(4):396-400.
17. Buschbaum M, Wender P. Average evoked responses in normal and minimally brain dysfunctioned children treated with amphetamine. *Arch Gen Psychiatry* 1973; 29(6):764-70.
18. Halliday R, Rosenthal JH, Naylor H, Callaway E. Averaged evoked potential predictors of clinical improvement in hyperactive children treated with methylphenidate: an initial study and replication. *Psychophysiology* 1976; 13(5):429-40.
19. Pritchard LS, Sutton S, Hakerem G. Evoked potentials in hyperkinetic and normal children under certainty and uncertainty: a placebo and methylphenidate study. *Psychophysiology* 1976; 13(5):419-28.
20. Cohen HL, Porjesz B, Begleiter H. EEG characteristics in males at risk for alcoholism. *Alcohol Clin Exp Res* 1991; 15(5):858-61.
21. Pollock VE, Gabrielli WF, Mednick A, Goodwin DW. EEG identification of subgroups of men at risk for alcoholism. *Psychiatry Res* 1988; 26(1):101-4.
22. Ehlers CL, Schuckit MA. EEG fast frequency activity in the sons of alcoholics. *Biol Psychiatry* 1990; 27(6):631-41.
23. Pollock VE, Volavka J, Goodwin DW, et al. The EEG after alcohol administration in men at risk for alcoholism. *Arch Gen Psychiatry* 1983; 40(8):857-61.
24. Struve FA, Straumanis JJ. Electroencephalographic and evoked potentials methods in human marijuana research: historical review and future trends. *Drug Develop Res* 1990; 20: 369-388.
25. Braverman ER, Blum K, Smayda RJ. A commentary on brain mapping in 60 substance abusers: can the potential for drug abuse be predicted and prevented by treatment? *Curr Ther Res* 1990; 48(4):569-585.

26. Struve F, Straumanis JJ. Separation of chronic marijuana (THC) users from nonusers: a discriminant function analysis using quantitative electroencephalographic variables. *Biol Psychiatry* 1990; 27:52A-53A.
27. Struve F, Straumanis JJ. Persistent topographic quantitative EEG changes in chronic marijuana (THC) use: a replication study. *Biol Psychiatry* 1989; 25:29A.
28. Abraham HD and Duffy FH. Computed EEG abnormalities in panic disorder with and without premorbid drug abuse. *Biol Psychiatry* 1991; 29(7):687-90.
29. Cadaviera F, Grau C, Roso M, Sanchez-Turet M. Multimodality exploration of event-related potentials in chronic alcoholics. *Alcohol Clin Exp Res* 1991; 15(4):607-11.
30. Begleiter H, Porjesz B. Potential biological markers in individuals at high risk for developing alcoholism (Review). *Alcohol Clin Exp Res* 1988; 12(4):488-93.
31. Begleiter H, Porjesz B. Neurological processes in individuals at risk for alcoholism (Review). *Alcohol* 1990; 25(2-3):251-6.
32. Maurer K, Dierks T, Strik WK, Frolich L. P3 topography in psychiatry and psychopharmacology. *Brain Topogr* 1990; 3(1):79-84.
33. Pfefferbaum A, Ford JM, White PM, Mathalon D. Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. *Alcohol Clin Exp Res* 1991; 15(5):839-50.
34. Noldy NE, Carlen PL, Santos CV. Quantitative EEG and P300 in cocaine withdrawal. *Brain Topography* 1990; 3(1):262-263.
35. Braverman ER, Smith R, Smayda R, Blum K. Modification of P300 amplitude and other electrophysiological parameters of drug abuse by cranial electrical stimulation. *Curr Ther Res* 1990; 48:586-596.
36. Whipple SC, Parke ES, Noble EP. An atypical neurocognitive profile in alcoholic fathers and their sons. *J Stud Alcohol* 1988; 49(3):240-4.
37. Parsons OA, Sinha R, Williams HL. Relationships between neuropsychological test performance and event-related potentials in alcoholic and nonalcoholic samples. *Alcohol Clin Exp Res* 1990; 14(5):746-55.
38. Garber HJ, Weilburg JB, Duffy FH, Manschreck TC. Clinical use of topographic brain electrical activity mapping in psychiatry. *J Clin Psych* 1989; 50(6):205-11.
39. American Psychiatric Association Task Force: Quantitative electroencephalography: a report on the present state of computerized EEG techniques. *Am J Psychiatry* 1991; 148(7):961-4.
40. Duffy FH, Hughes JR, Miranda F, Bernad P, Cook P. Status of quantitative EEG (QEEG) in clinical practice, 1994. *Clin Electroencephalogr* 1994;25(4):VI.
41. Mehra IV. The electroencephalograms: its patterns and origins. *JAMA* 1994; 272(17):1325-1326.
42. Riley T. *JAMA* 1994. 271:1456. Review of Barlow JS, (ed). *The Electroencephalograms: its patterns and origins*. Cambridge, Mass: MIT Press, 1993.
43. Post RM, Trimble MR, Pippenger CE. Use of anticonvulsants in the treatment of manic-depressive illness. *Clin Use of Anticonvulsants in Psychiatric Disorders*. Demos Publications 1989: 113-153.
44. Post RM, Trimble MR, Pippenger CE. Anticonvulsants as adjuncts to neuroleptics in the treatment of schizoaffective and schizophrenic patients. *Clin Use of Anticonvulsants in Psychiatric Disorders*. Demos Publications 1989: 153.
45. Post RM, Trimble MR, Pippenger CE. Anticonvulsants in the treatment of aggression and dyscontrol. *Clin Use of Anticonvulsants in Psychiatric Disorders*. Demos Publications 1989: 165.
46. Koob GF, Voocurino FJ, Amaric M. Neurochemical substrates for opiate reinforcement. In: Fisher S, Raskin A, Uhlenhuth EH, (eds). *Aspects*. New York: Oxford University Press, 1987:80-108.
47. Blum K, Kozlowski GP. Ethanol and neuro-modulator interactions: a cascade model of reward. In: Ollat H, Parvez S, Parvez H, (eds). *Progress In Alcohol Research*. 1990b: 131-147.
48. Ballenger JC, Post RM. Carbamazepine in manic-depressive illness: a new treatment. *Am J Psychiatry* 1980; 137(7):782-90.
49. Goldstein RB, Especially MM, Adams PB, et al. Psychiatric disorders in relatives of probands with panic disorder and/or major depression. *Arch Gen Psychiatry* 1994; 51(5):383-94, Division of Clinical and Genetic

- Epidemiology, New York State Psychiatric Institute, NY.
50. Brown GW, Hines JC, Fisher P, Ray DS. Isolation of the genes encoding the 51-kilodalton and 28-kilodalton subunits of crithidia fasciculata replication protein A. University of London. Mol Biochem Parasitol Jan 1994; 63(1):135-42.
  51. Abbott JP, Weller SB, Walker RS. Psychiatric disorders of opioid addicts entering treatment: preliminary data. J Addictive Diseases 1994; 13(3):1-12.
  52. Gerez M, Tello A. Clinical significance of focal topographic changes in the electroencephalogram (EEG) and evoked potentials (EP) of psychiatric patients. Brain Topogr 1992; 5(1):3-10.
  53. Halikas JA, Kuhn KL, Crea, FS, et al. Treatment of crack cocaine use with carbamazepine. Am J Drug Alcohol Abuse 1992; 18(1):45-56.
  54. Chu NS. Carbamazepine: prevention of alcohol withdrawal seizures. Neurology 1979; 29(10):1397-1401.
  55. Mott SH, Packer RJ, Soldin SJ. Neurologic manifestations of cocaine exposure in childhood. Pediatrics. 1994; 93(4):557.
  56. Stuppaek CH, Pycha R, Miller C, Whitworth AB, et al. Carbamazepine versus oxazepam in the treatment of alcohol withdrawal: a double-blind study. Alcohol 1992; 27(2):153-8.
  57. Campbell J.L., et al. Impact on desipramine or carbamazepine on patient retention in outpatient cocaine treatment: preliminary findings. J Addictive Diseases 1994; 13(4):191-199.
  58. Latkin CA, Mandell W. Depression as an antecedent of frequency of intravenous drug use in an urban, nontreatment sample. Inter J Addictions 1993; 28(14):1601-12.
  59. Maier W, Minges J, Lichtermann D. Alcoholism and panic disorder: co-occurrence and co-transmission in families. Eur Arch Clin Neuroses 1993; 243:205-11.
  60. Dinwiddie SH, Reich T, Cloninger CR. Psychiatric comorbidity and suicidality among intravenous drug users. J Clin Psychiatry 1992; 53(10):364-9.
  61. Brown SA, Inaba RK, Gillin JC, Schuckit MA, Stewart MA, Irwin MR. Alcoholism and affective disorder: clinical course of depressive symptoms. Am J Psych 1994; 152(1):45.
  62. Holmes TH, Rahe RH. The social readjustment rating scale. J Psychosomatic Res 1967; 11(2):213-18.
  63. Fendrich M, Mackesy-Ami ME. Inconsistencies in lifetime cocaine and marijuana use reports: impact on prevalence and incidence. Society for the Study of Addiction to Alcohol and Other Drugs 1995; 90:111-118.
  64. Miller NS. Issues in the diagnosis and treatment of comorbid addictive and other psychiatric disorders. Direction in Psychiatry. The Hatherleigh Co. Ltd. 1994; 14(25).
  65. Blum K, Noble EP, Sheridan PJ, et al. Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA 1990; 263(15):2055-60.
  66. Blum K, Noble EP, Sheridan PJ, et al. Association of the A1 allele of the D2 dopamine receptor gene with severe alcoholism. Alcohol 1991; 8(5):409-16.
  67. Blum K, Noble EP, Sheridan PJ, et al. Genetic predisposition in alcoholism: association of the D2 dopamine receptor TaqI B1 RFLP with severe alcoholics. Alcohol 1993; 10(1):59-67.
  68. Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. Epilepsy Res 1990; 5(1):49-60.
  69. Blom JL, Anneveldt M. An electrode cap tested. Electroencephalogr Clin Neurophysiol 1982; 54(5):591-4.
  70. Blom JL, and Mechelse K. The EEG profile. in: Lechner H, Aranibar A, (eds). EEG and Clinical Neurophysiology, Excerpta Medica, Int Congr Ser 526. Amsterdam; 1980: 338-46.
  71. Klass DD, Sharborough FW. Electroencephalography. In: Aronson E, Auger RG, Easton JS, et al, (eds). Clinical examination in neurology. Mayo Clinic and Mayo Foundation 5th ed. Philadelphia; WB Saunders, 1981; 278-99.
  72. Duffy FH, Albert MS, McAnulty G, Garvey AJ. Age-related differences in brain electrical activity of healthy subjects. Ann Neurol 1984; 16(4):430-8.
  73. Barajas JJ. The effects of age on human P3 latency. Acta Otolaryngol (Stockh) 1991. (suppl); 476:157-160.
  74. Maus A, Endresen J. Misuse of computer-generated results. Med Biol Eng Comput 1979; 17:126-129.

75. Abt K. Problems of repeated significance testing. *Controlled Clinical Trials* 1981; 1:377-381.
76. Abt K. Significance testing of many variables - problems and solutions. *Neuropsychobiol* 1983;9:47-51.
77. Oken BS, H. CK. Statistical issues concerning computerized analysis of brainwave topography. *Ann Neurol* 1986;19:493-494.
78. Duffy FH. Clinical decision making in quantified electroencephalographic analysis. In: Samson-Dollfus D, Gotman J, Guieu JD, Etevenon P (eds). *Statistics and Topography in Quantitative EEG*. Paris:Elsevier, 1988:9-26.
79. Coste J, Fermanian J, Venot A. Methodological and statistical problems in the construction of composite measurement scales: a survey of six medical and epidemiological journals. *Statistics in Medicine* 1995;14:331-345.
80. Bartels PH. Numerical evaluation of cytologic data VIII. Computation of the principal components. *Annal Quant Cytol* 1981;3:83-90.
81. Bartels PH. Numerical evaluation of cytologic data IX. Search for data structure by principal components transformation. *Annal Quant Cytol* 1981; 3:167-177.
82. Duffy F, Jones K, Bartels P, McAnulty G, Albert M. Unrestricted principal components analysis of brain electrical activity; issues of data dimensionality, artifact, and utility. *Brain Topogr* 1992;4:291-307.
83. Mayberg HS. Frontal lobe dysfunction in secondary depression. *J Neuropsychiatry Clin Neurosciences* 1994; 6:428-442.
84. Braverman ER. Brain electrical activity mapping (BEAM) in patients who commit violent crimes: are bitemporal abnormalities a characteristic? *J Orthomolecular Med* 1993; 8(3):54-6.
85. Miller NS, Hoffmann NG. Depression associated with alcohol/other drug addiction. *J Addiction* 1994; 13(2).
86. Ziedonia DM, Rayford BS, Bryant KJ, Rounsaville BJ. Psychiatric comorbidity in white and African-American cocaine addicts seeking substance abuse treatment. *Hospital Community Psychiatry* 1994; 45(1).
87. Westermeyer J, Specker S, Neider J, Lingenfelter MA. Substance abuse and associated psychiatric disorder among 100 adolescents. *J Addictive Diseases* 1994; 13(1).
88. Wills TA, Vaccaro D, Schreiber D, Benson G. Psychosocial predictors of early-onset substance use. *Ann Behavioral Med* 1994; 16.
89. McCormick LH. Mothers of children with attention deficit are at risk of depression. *American Academy of Family Physicians* 1995; 657.
90. Biederman J, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *Am J Psychiatry* 1993; 150:1792-1798.
91. Blackwood DH, Muir WJ. Cognitive brain potentials and their application (Review). *Br J Psychiatry Suppl* 1990; 157(9):96-101.
92. Jacobson SA, Leuchter AF, Walter DO. Conventional and quantitative EEG in the diagnosis of delirium among the elderly. *J Neurol Neurosurg Psychiatry* 1993; 56(2):153-8.
93. Blum K, Braverman ER, Wood RC, Sheridan PJ, DRD2 A1 allele and P300 abnormalities in obesity (abstract). Presented at the American Society of Human Genetics meeting, Montreal, Canada, October 28. *Am J Hum Genet* 1994.
94. Cornellus JR, Salloum IM, Mezzich J, et al. Disproportionate suicidality in patients with comorbid major depression and alcoholism. *Am J Psychiatry* 1995; 152:3.
95. Perryman KM, Fitten LJ. Impact of attentional deficits on driving performance of the elderly and individuals with mild Alzheimer's disease. *Facts Res Gerontology* 1994; 409-420.
96. Wolfe N, Reed BR, Eberling JL, Jagust WJ. Temporal lobe perfusion on single photon emission computed tomography predicts that rate of cognitive decline in Alzheimer's disease. *Arch Neurol* 1995; 52(3).
97. Koshino Y, Muata T, Oomori M, Horie T, Isaki K, Tsubokawa M, Hamada T, Fukui J. Temporal minor slow and sharp activity in psychiatric patients. *Clin Electroencephalogr* 1990; 21(4):225-232.
98. Kowell A. A referring physician's view of neurological assessment. Fifth Annual International PET Conference. McClean, Virginia. October 28-31, 1993.

99. Porjesz B, Begleiter H, Bihari B, Kissin B. N2 component of the event-related brain potential in abstinent alcoholics. *Electroencephalogr Clin Neurophysiol* 1987; 66(2):121-31.
100. Rockstroh B, Elbert T, Lutzenberger W, Altenmüller E. Effects of the anticonvulsants benzodiazepine clonazepam on event-related brain potentials in humans. *Electroencephalogr Clin Neurophysiol* 1991; 78(2):142-9.
101. Kirby AW, Wiley RW, Harding TH. Cholinergic effects on the visual evoked potential. *Evoked Potential* 1986; 26:296-306.
102. Fukuda M, Hiramatsu K, Honda M, et al. Shortening of N1 and P3 latencies in event-related potentials observed coincidentally with clinical improvement during nootropic medication in a demented patient: specific effect of nicergoline. *Jpn J Psychiatry Neurol* 1992; 46(4):919-25.
103. Maurer K, Dierks T, Laux G, et al. Topographic mapping of EEG and auditory evoked P300 in neuropsychopharmacology (topographic pharmaco-EEG and pharmaco-AEP 300). *Pharmacopsychiatry* 1988; 21(6):338-42.
104. Maurer K, Dierks T, Strik WK, Frolich L. P3 topography in psychiatry and psychopharmacology. *Brain Topogr* 1990; 3(1):79-84.
105. DeFrance JF, Hymel C, Trachtenberg MC, et al. Enkephalinase-inhibition and precursor amino acid loading enhances attention processing and P300 in healthy humans. *Amer Psychiatric Electrophysiology Assoc, 2nd Annual Meeting, Philadelphia, PA, May 20, 1994.*
106. Thatcher RW, Fishbein DH. Computerized EEG, nutrition and behavior. *J Applied Nutrition* 1984; 36(2):81-92.
107. Epstein CM, Trotter JF, Averbook A, et al. EEG mean frequencies are sensitive indices of phenylalanine effects on normal brain. *Electroencephalogr Clin Neurophysiol* 1989; 72(2):133-9.
108. Araki SA, Muata K, Yokoyama K, Uchida E. Auditory event-related potential (P300) in relation to peripheral nerve conduction in workers exposed to lead, zinc, and copper: effects of lead on cognitive function and central nervous system. *Am J Ind Med* 1992; 21(4):539-47.
109. Lester ML, Horst RL, Thatcher RW. Protective effects of zinc and calcium against heavy metal impairment of children's cognitive function. *Nutrition Behavior* 1986; 3:145-61.
110. Christensen L, Bourgeois A, Cockcroft R. Dietary alteration of somatic symptoms and regional brain electrical activity. *Biol Psychiatry* 1991; 29(7):679-82.
111. Peniston EG, Kulkosky PJ. Alpha-theta brain-wave training and beta-endorphin levels in alcoholics. *Alcohol Clin Exp Res* 1989; 13(2):271-9.
112. Pockberger H, Rappelsberger P, Petsche H, et al. Computer-assisted EEG topography as a tool in the evaluation of actions of psychoactive drugs in patients. *Neuropsychobiology* 1984; 12(2-3):183-7.
113. Itil TM, Eralp E, Itil KZ, et al. CEEG dynamic brain mapping: a new method to evaluate brain function in different psychological and drug conditions. *Symposium Electric and Magnetic Activity of the CNS: Research and Clinical Application in Aerospace Medicine. Advisory Group for Aerospace Research and Development, 1987.*
114. Sloan EP, Fenton GW, Standage KP. Anticholinergic drug effects on quantitative electroencephalogram, visual evoked potential, and verbal memory. *Biol Psychiatry* 1992; 31(6):600-6.
115. Nobilio D, et al. Effect of levo-acetyl-carnitine on P300 potential. *Curr Ther Res* 1990; 47:267-77.
116. McNamara ME. Advances in EEG-based diagnostic technologies. In: Stoudemire A, Fogel BS, (eds). *Med Psych Practice. Vol. 1.* Washington, DC: American Psychiatric Press, 1991: 163-89.
117. Pollock VE, Schneider LS. Quantitative, walking EEG research on depression. *Society Biological Psychiatry* 1990; 27:257-780.
118. Morihisa JM, McNulty GB. Structure and function: brain electrical activity mapping and computed tomography in schizophrenia. *Biol Psychiatry* 1985; 20:3-19.
119. Benson DF. The role of frontal dysfunction in attention deficit hyperactivity disorder. *J Child Neurology* 1991; 6:S9-S12.
120. Mann CA, Lubar JF, Zimmerman AW, Miller CA, Muenchen RA. Quantitative analysis of EEG in boys with attention-deficit-hyperac-

- tivity disorder: controlled study with clinical implications. *Pediatric Neurology* 8(1):30-36
121. Noble EP, Syndulko K, Fitch RJ, et al. D2 receptor TAQ I alleles in alcoholic and nonalcoholic patients. *Alcohol and Alcoholism* 1994, in press.
  122. Parsian A, Todd RD, Devor EJ, et al. Alcoholism and alleles of the human D2 dopamine receptor locus: studies of association and linkage. *Arch Gen Psychiatry* 1991; 48(7):655-63.
  123. Arinami T, Itokawa M, Komiyama T, et al. Association between severity of alcoholism and the A1 allele of the dopamine D2 receptor gene TAQ I A RFLP (in Japanese). *Biol Psychiatry* 1993; 33(2):108-14.
  124. Amadeo S, Abban M, Fourcade ML, et al. D2 dopamine receptor gene and alcoholism. *J Psychiatr Res* 1993; 27(2):173-9.
  125. Cook CC, Holmes D, Breh P, et al. Linkage analysis confirms a genetic effect at the D2 dopamine receptor locus in heavy drinking and alcoholism. *Neuropsychogenetics* (in press).
  126. Smith SS, O'Hara BF, Persico AM, et al. Genetic vulnerability to drug abuse: the D2 dopamine receptor Taq I B1 restriction fragment length polymorphism appears more frequently in polysubstance abusers. *Arch Gen Psychiatry* 1992; 49(9):723-7.
  127. Noble EP, Blum K, Khalsa ME, et al. Allelic association of the D2 dopamine receptor gene with cocaine dependence. *Drug Alcohol Depend* 1993; 33(3):271-85.
  128. Comings DE, MacMurray J, Johnson JP, et al. The dopamine D2 receptor gene: a genetic risk factor in polysubstance abuse. *Drug Alcohol Dependence* (in press).
  129. Uhl G, Blum K, Noble E, Smith S. Substance abuse vulnerability and D2 receptor genes. *Trends Neurosci* 1993; 16(3):83-8.
  130. Comings DE, Comings BG, Muhleman D, et al. The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. *JAMA* 1991; 266(13):1793-800.
  131. Noble EP, Noble RE, Ritchie T, et al. Allelic association of the D2 dopamine receptor gene with obesity. *Int J Eating Disorders* 1994 (in press).
  132. Noble EP, Blum K, Ritchie T, et al. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Arch Gen Psychiatry* 1991; 48(7):648-54.
  133. McBride NJ, Chénet E, Dyr W, et al. Densities of dopamine D2 receptors are reduced in CNS regions of alcohol-preferring P rats. *Alcohol* 1993; 10(5):387-90.
  134. Berman SM, Whipple SC, Fitch RJ, Noble EP. P3 in young boys as a predictor of adolescent substance use. *Alcohol* 1993; 10(1):69-76.
  135. Noble EP, et al. Prolonged P300 latency in children with the D2 dopamine receptor A1 allele. *Am J Hum Genet* 54: 658-668.
  136. Lawford Br, Young RM, Rowell Qualichefski J, et al. Bromocriptine in the treatment of alcoholics with the D2 dopamine receptor A1 allele. *Nature Medicine* 1995.
  137. Blum K, Braverman ER, Dinardo MJ, Wood RC, Sheridan PJ. Prolonged P300 latency in a neuropsychiatric population with the D2 Dopamine receptor A1 allele. *Pharmacogenetics* 1994; 4:313-322.
  138. Christian JC, Edenburg H, O'Connor SJ, et al. Associations of dopamine D2 polymorphisms with brain electrophysiology. *Alcoholism* 1994; 18(2): 178 (abstract).
  139. Blum K, Sheridan PJ, Wood RC, et al. Dopamine D2 receptor gene variants: association and linkage studies in impulsive-addictive-compulsive behaviour. *Pharmacogenetics* 1995;5: 121-141.
  140. Lovinger DM, Grant KA. Alcohol neurotoxicity: effects and mechanisms. *Handbook of Neurotoxicology*.
  141. Seiden LS, Sabol KE. Neurotoxicity of methamphetamine-related drugs and cocaine. *Handbook of Neurotoxicology*.
  142. Teens' drug use rises as perceived risk drops. *The Wall Street Journal*, Jan 1995.
  143. Hudson J. Drug abuse increases among U.S. teenagers as beliefs about drugs' dangers soften. *Psychiatric Times*, Feb 1995;35-36.
  144. Gordon HW. Human neuroscience at National Institute on Drug Abuse: implications for genetics research. *Am J Med Gen* 1994;54:300-303.
  145. Neiswanger K, Hill S.Y., Kaplan BB. Association between alcoholism and the TAQ I A



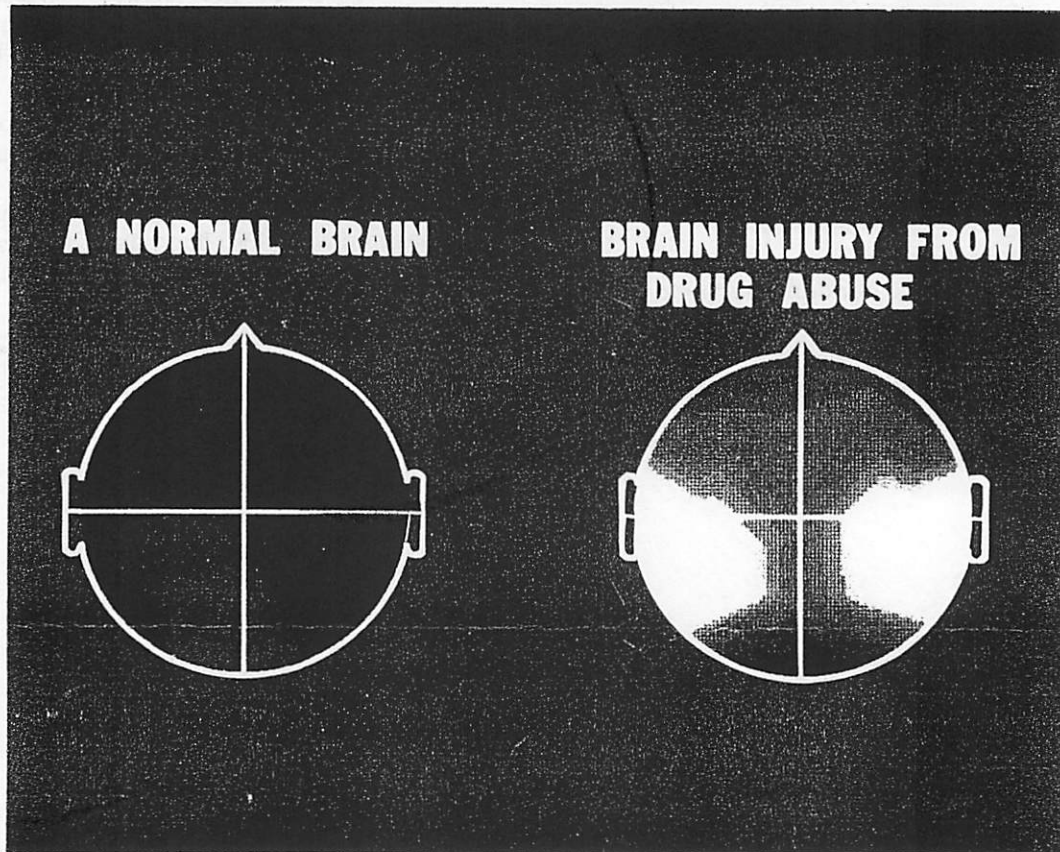
- RFLP of the dopamine D2 receptor gene in the absence of linkage. *Psychiatric Genetics*, 1993; 3:130 (abstract).
146. Neiswanger K, Hill S, S.Y., Kaplan BB. Association between alcoholism and the TAQ1A RFLP of the dopamine D2 receptor gene in the absence of linkage. *Neuropsychiatric Genetics*, *Am J Med Gen*, 1995 (in press).
147. Kokkevi A, Stefanis C. Drug abuse and psychiatric comorbidity. *Com Psych*, 1995;36(5):329-337.
148. Nynes EV, McGrath PJ, Quitkin FM. Treating anxiety in patients with alcoholism. *J Clin Psychiatry* 1995;56(2)
149. Monahan J. Violence among mentally ill found to be concentrated among those with comorbid substance abuse disorders. *Psychiatric News*. Dec, 1995.
150. Adams KM, Gilman S, Koeppe RA. Neuropsychological deficits are correlated with frontal hypometabolism in positron emission tomography studies of older alcoholic patients. *Alcoholism: Clin Exp Res*. 1993;17(2).
151. Gilman S, Adams K, Koeppe RA, et al. Cerebellar and frontal hypometabolism in alcoholic cerebellar degeneration studies with positron emission tomography. *Annals Neurology* 1990; 28(6).
152. Adams KM, Gilman S, Koeppe R, et al. Correlation of neuropsychological function with cerebral metabolic rate in subdivisions of the frontal lobes of older alcoholic patients measured with (18F) fluorodeoxyglucose and positron emission tomography. *Neuropsychology* 1995;9(3):275-280.
153. Blum K, Cull JC, Braverman ER, Comings DE. Reward Deficiency Syndrome. *American Scientist*, 1996; 84: 132-145.



## Appendix

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The following figure is included as another example of brain dysfunction caused by drug abuse. This material is for Drug Education Programs.



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