

P300 and Neuropsychological Assessment in a Sample of Non Alcoholic Egyptian Drug Abusers

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Abstract

This study attempted to assess cognitive functions using auditory P300 event related potentials and neuropsychological evaluation. This was done in a case-control design and the sample consisted of 32 subjects with a DSM-IV diagnosis of substance dependence and 30 control subjects. No significant differences were found between the two groups. However, benzodiazepine dependent subjects had more prolonged P300 latency when compared with opioid dependent subjects. Duration of addiction correlated with P300 latency and scores of both Bender Gestalt and Trail Making (B) tests. Research in this area is still in its beginning, and the results of this study are in line with similar recent ones. Evidence from these studies revealed cognitive impairment due to prolonged substance abuse.

Rational & Background

Cognitive abnormalities have been studied in different psychiatric disorders using neurophysiological measures. Among these approaches are the brain event-related potentials (ERPs). Incoming sensory stimuli are associated with brief changes in brain potentials, and these can be detected when suitable averaging stimuli are used to demarcate them from the background EEG activity. Successive epochs of EEG are summated and averaged by computer while repeated visual, auditory or somatosensory stimuli are presented to the subject. The ERPs recorded using this method can be divided into early and late components. The principle interest of psychiatry, however, centers on the late components of ERPs elicited while the subject is engaged in some simple task (cognitive ERPS) (Lishman, 1998).

Among the late components or cognitive ERPS, the large late positive component occurring some 300 m.s. after stimulus presentation (P300) has been the most widely studied in relation to psychiatric disorders. P300 is an objective measure of

selective attention and mental tracking; it is regarded as the neurophysiological correlate of cognitive functions such as decision making, information processing and short-term memory. P300 abnormalities have been demonstrated in a variety of psychiatric disorders: dementia, schizophrenia, mania, depressive illness and attention deficit hyperactivity disorder. P300 is affected by age, task difficulties, I.Q., drugs and attention (Lishman, 1998). In case of substance abuse, several investigators studied the effects of substance abuse on cognitive functioning using the P300 component. Different substances were studied e.g. opiates (Kouri et al, 1996), benzodiazepines (Urata et al, 1996) cocaine (Kouri et al, 1996; Easton & Bauer, 1997), methamphetamine (Winsberg et al, 1997; Iwanami et al, 1998), and marihuana (Patrick et al, 1995; 1997). However, the most frequently and most extensively studied substance in this context is alcohol (Pfefferbum et al, 1979; Ohta & Ogura, 1997; Porjesz et al, 1998; Ji J. et al, 1999). In Egypt, few, if any studies

of ERPs have been done in non-alcoholic substance abusers.

This study is essentially exploratory and aims to assess cognitive functions in a sample of Egyptian non-alcoholic drug abusers using P300 and neuropsychological measures.

Subjects and Methods

The study was conducted in a case-control cross sectional design, 32 substance dependent subjects were compared with 30 matched control subjects. All consecutive admissions to a private hospital during a 6-month period were assessed.

Cases were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (American Psychiatric Association 1994). They were all males who abstained at least 4 weeks before the study (confirmed by serum and urine drug free samples). They included subjects from consecutive admissions to a private hospital without any of the following: other axis I disorder, alcohol abuse, neurological disease, head trauma, difficulty in hearing or other medical problems. Controls consisted of 30 subjects matched for age, sex and education with no psychiatric disorder, history of alcohol or substance abuse, medical disorder nor difficulty in hearing.

Assessment Tools & Procedures

Clinical Assessment

All subjects underwent a full psychiatric and neurological assessment (history and clinical examination) to ensure that they met the DSM-IV criteria and to exclude any comorbid neurological disorder that may confound the results.

Neuophysiological Measures

P 300 Event-related Potential

P300 auditory evoked potentials were recorded using a two-tone auditory odd ball paradigm. A 3-channel computer averager (Amplaid MK15) was used to record the response. P300 was recorded at the PZ as an active electrode with a reference at the ipsilateral ear according to the 10-20 international system of electrode placement. The electrode impedance was kept at below 5k ohm. The hearing threshold for each subject was determined. In each trial, an auditory tone of 1000 Hz and 2000 Hz (representing the rare and frequent stimuli) was presented. A total of 200 auditory trial tones were presented to the ears through earphones with duration of 4 msec and intensity of 50 db above hearing threshold. The subject was instructed to press a switch with his thumb as quickly as possible whenever hearing the infrequent tone.

For each subject, P300 latency and amplitude were recorded and reaction time was measured. Generally the first positive peak after 250 msec was measured. The latency in (msec) was measured by moving the computer cursor to the highest point at the peak. In case of double peaks, the latency point was selected as the mid-point, determined by extending the ascending and descending limbs of the waves. Amplitude of the wave (in microvolts) was measured from the peak to the base line of the trace.

Neuropsychological Assessment

Each subject was administered the following tests to detect early or minimal cognitive impairment:

Bender Gestalt Test

The test is used as a screening instrument to screen for generalised cognitive impairment. It assesses two functions

considered most sensitive to cerebral dysfunction, perception of spatial relations and memory for newly learned material (Lezak, 1995).

Trail Making Test (A) and (B)

The test has demonstrated excellent differentiation between brain-damaged and nonbrain-damaged subjects. Performance on the test requires spatial analysis, motor control, alertness, concentration and ability to shift attention between alternatives (Lezak, 1995).

Wechsler Adult Intelligence Scale (WAIS)

The Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1958) is a standardised instrument for the measurement of intelligence, providing separate scores of verbal and performance abilities. It consists of 11 subtests, each of which assesses a certain area of functioning. Comprehension assesses common sense verbal reasoning, picture completion requires perceptual reasoning, the similarities subtest measures the ability to make verbal abstraction by asking the similarity between objects or concepts. The arithmetic subtest involves problem solving while picture arrangement examines sequential reasoning for pictures. Block design and object assembly subtests assess visuospatial analysis and problem solving of block design and puzzles. Statistical Analysis

For descriptive purposes, mean and standard deviation were used and for comparative purposes, the Student test (unpaired, two tailed) was used. Pearson's correlation coefficient (r) was used to examine relationship between 2 parameters. Statistical analysis was done according to Ingelfinger et al (1994) and Knapp and Miller (1992).

Result

All cases were males having age range from 18 to 40 years with a mean of 29.9 ± 6.2 years. The mean duration of addiction was 5.41 ± 3.8 years (1 to 14 years). Half of the cases ($N = 16$) were opioid (Heroin) abusers while the other half ($N = 16$) abused benzodiazepines. The results were compared with that of normal controls having mean age of 30.2 ± 5.4 years.

Regarding P300 parameters, there were no statistically significant differences between substance dependent subjects -as a whole- and normal controls (Table 1). On the other hand, benzodiazepine dependent subjects had significantly more delayed P300 latency when compared with opioid dependent subjects. No significant difference was found between both groups in P300 amplitude and reaction time (Table 2). Results of different neuropsychological tests in cases and controls were illustrated in table (3). No statistically significant difference could be detected in various tests used when comparing cases -as a whole- and normal controls. Even after classifying cases into benzodiazepine dependent and opioid dependent subgroups, no difference was found in any of neuropsychological tests (Table 4).

There was a statistically significant correlation between duration of substance abuse and P300 latency (Table 5). Moreover, a significant correlation was found between duration and scores of both Bender Gestalt and Trail Making (B) tests. Correlating P300 parameters and different neuropsychological tests revealed a significant correlation between P300 latency and Bender Gestalt test score. In addition, reaction time was correlated with scores of both Bender Gestalt and Trail Making (B) tests (Table 6).

Table (1) : Shows means + SD of parameters in cases & controls.

P 300 Parameters	Cases		Controls		P value
	Mean	S.D	Mean	S.D	
Latency	317.68	42.68	317.52	21.19	NS
Amplitude	5.78	4.76	5.65	2.47	NS
Reaction Time	367.5	58.62	354.41	61.3	NS

NS: Non significant ($P>0.05$).

Table (2): Shows means + SD 300 parameters in benzodiazepine and opioid dependent subjects.

P 300 Parameters	Benzodiazepine		opioid		P value
	Mean	S.D	Mean	S.D	
Latency	334.13	40.8	301.23	44.56	<0.05
Amplitude	5.36	4.91	6.2	4.61	NS
Reaction Time	369	56.84	366	60.4	NS

$P<0.05$ = Significant difference.

Table (3) : Illustrates means + SD of neuropsychological tests in cases & controls.

Test	Cases		Controls		P value
	Mean	S.D	Mean	S.D	
Bender Gestalt	19.23	3.78	21.18	4.22	NS
Trail Making (A)	59.64	16.66	52.21	19.63	NS
Trail Making (B)	131.09	59.24	122.29	55.49	NS
I.Q	102.09	9.03	109.22	8.22	NS
Deterioration Index	13.68	8.95	12.26	7.49	NS

NS : Non significant ($P>0.05$).

Table (4): Illustrates means + SD of neuropsychological tests in benzodiazepine and opioid dependent subjects.

Test	Benzodiazepine		Opioid		P value
	Mean	S.D	Mean	S.D	
Bender Gestalt	17.23	3.46	20.54	4.1	NS
Trail Making (A)	60.81	17.2	58.47	16.12	NS
Trail Making (B)	133.02	60.19	129.16	58.29	NS
I.Q	99.8	7.42	104.38	8.11	NS
Deterioration Index	14.2	8.92	13.16	7.99	NS

NS : Non significant ($P>0.05$).

Table (5) : Shows correlation coefficient (r) between duration of addiction and P300 Parameters and scores of neuropsychological tests.

	Duration
P300 Latency	0.39 **
P300 Amplitude	0.113
Reaction time	0.08
Bender Gestalt	-0.662 **
Trail Making (A)	0.093
Trail Making (B)	0.329 **

**** Significant Correlation.**

Table(6): Shows correlation coefficient (r) between P300 parameters and scores of neuropsychological tests.

	Bender Gestalt	Trail Making (A)	Trail Making (B)
P300 Latency	-0.32 **	0.08	0.2
P300 Amplitude	0.211	-0.05	0.03
Reaction Time	-0.29	0.06	0.36 **

**** Significant Correlation.**

Discussion

The results of this study showed no significant differences between non-alcoholic drug abusing subjects -as a whole- and a control group on neurophysiological and neuropsychological measures of cognitive impairment. There is more than one possible explanation for these results, most of them have to do with two issues: methodological approaches and replicated results from other similar studies in this field of research.

The results of studies targeting the effects of different drugs on P300 ERP in drug abusers have produced inconsistent findings. Patrick et al (1995) in an initial uncontrolled study reported reduction of P300 amplitude in marihuana users compared to controls.

However, in a more recent controlled study (Patrick et al, 1997) no significant differences could be found. In a study of P300 ERP in chronic methamphetamine dependence, Iwanami et al, (1998) reported delayed P300 latencies but normal amplitudes. Viewed from this perspective our results are not different from those of other investigators who used a P300 auditory odd-ball paradigm to investigate the effects of different drug effects on P300 ERPs in a cross sectional design.

In this study, P300 latency was significantly delayed in benzodiazepine dependent subjects compared with opioid dependent subjects. P300 latency was significantly

prolonged in subjects taking triazolam (Urata et al, 1996), alprazolam (Semlitsch et al 1995), and temazepam (Martin et al, 1992).

As regards neuropsychological assessment, the results from different studies in the literature are also inconsistent. The most consistent findings of neuro-psychological abnormalities in drug abusers compared to control subjects, come from recent studies of cocaine and alcohol abusers (Easton & Bauer, 1997; Gillin et al, 1998) who were not part of the sample in this study. Studies on subjects abusing other drugs have failed to date to demonstrate sufficient evidence of any consistent long-term neuropsychological abnormality with prolonged drug use (Gillin et al, 1998). On the other hand, a recent study on cannabis found significant difference between users and normal controls in attention (Elwan et al, 1997).

This study failed to demonstrate any differences between non-alcoholic drug abusers and controls on neuropsychological measures of cognitive functioning. Evidence from this study is similar to that from other studies of effects of drugs of abuse with the exception of alcohol and recently cocaine (Pope et al, 1995). The evidence from these studies is as yet insufficient to support or refute a prolonged effect of these drugs on cognitive functions that persists after detoxification (Gillin et al, 1998). This takes us to the next important issue concerning methodology and future recommendations in this field of research.

The sample size in this study was small, although characteristic of studies of

biological research on psychiatric patients in general, a low sample size would have detrimental effects on statistical power. The statistical power of a study is the probability of rejecting the null hypothesis when it is false or the likelihood of detecting any existing differences. When the sample size is low, the statistical power or the probability of detecting any significant difference becomes also low. This increases the risk of type II error i.e. rejecting the null hypothesis when it is false (Edmonstone & Freeman, 1992).

The design of this study was cross-sectional comparing between cases and controls. An alternative design worthy of pursuit in future studies is the prospective longitudinal design. This entails neuropsychological and neurophysiological assessment before and after detoxification in the same group of subjects with subsequent long-term follow-up. Another important point to put into consideration is assessment tools or outcome measures of neurophysiological and neuropsychological functioning. For example, more specific tests of cognitive processing rather than screening tests for generalised cognitive impairment might be more likely to detect subtle cognitive deficit. This study revealed significant correlation between duration of addiction and P300 latency and scores of both Bender Gestalt and Trail Making (B) tests. This confirmed the importance of P300 parameters especially latency in evaluation of cognitive function. Other important dimensions worthy of consideration in future studies, is the relationship between cognitive deficit and severity and duration of addiction. More important is the effect of this cognitive deficit

on treatment response, social and vocational functioning and prognosis.

This study is among few of the recent studies trying to determine the effect of drugs of abuse other than alcohol on neurophysiological and neuropsychological dimensions of cognitive functioning in drug abusers. Research in this field is still in its beginning and evidence from this study can be added to that from other similar ones aiming at throwing more light on effects of drug abuse on cognitive functioning in non-alcohol drug abusers. P300 latency is very sensitive objective tool, which could detect cognitive impairment especially in benzodiazepine dependent subjects.

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تقويم الموجة ب ٣٠٠ والقياسات النفسية العصبية
لدى عينة من المصريين مدمنى المخدرات لغير الكحوليات

قامت هذه الدراسة بتقويم الوظائف المعرفية باستخدام الموجة ب ٣٠٠ وقياسات نفسية وعصبية حيث اشتملت على ٣٢ شخصا مدمنا و ٣٠ شخصا من الأصحاء. وفى حين لم يظهر فرق ذو دلالة إحصائية بين المدمنين والأصحاء كان هناك تأخر فى الموجة ب ٣٠٠ عند مدمنى عقار البنزوديازيبين عند مقارنتهم بدمنى المخدرات الهيروين ، كما ظهرت علاقة ذات دلالة إحصائية بين طول فترة التعاطى وكل من تأخر ظهور الموجة ب ٣٠٠ والتدهور فى الاختبارات النفسية والعصبية. وهكذا تدهورت هذه الدراسة قد أكدت التدهور فى لوظائف المعرفية الناتج من التعاطى لمدة طويلة مما يتوافق مع العديد من الدراسات الحديثة فى هذا المجال.