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Visual P300: An Interlaboratory Consistency Study

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From the Departments of Psychiatry at *SUNY Health Science Center, Brooklyn, NY;
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COHEN, H. L., W. WANG, B. PORJESZ, L. BAUER, S. KUPERMAN, S. J. O'CONNOR, J. ROHRBAUGH AND H. BEGLEITER. *Visual P300: An interlaboratory consistency study.* ALCOHOL 11(6) 583-587, 1994. — The P300 component of the event-related potential is reduced in both abstinent alcoholics and in males at high risk for developing alcoholism. Here, 96 males ($\bar{X} = 22.1$ years) who were part of an interlaboratory ($n = 6$) consistency study in the national COGA (Collaborative Study on the Genetics of Alcoholism) Project were subjects in a visual target selection paradigm. Each of the participating laboratories used the same experimental design, hardware and software. Each subject received a randomized series of target, nontarget and novel visual stimuli, and upon detecting the target stimulus, was required to make a button press as quickly as possible. Statistical analyses indicated that there were no significant differences in P300 amplitude and latency at the Pz electrode under any of the aforementioned conditions across laboratories. Thus, the interlaboratory consistency of the visual P300 indicates that it may be of utility in a national collaborative study on the genetics of alcoholism.

Visual P300 Event related potential Consistency

ELECTROPHYSIOLOGICAL investigations into the consequences of chronic ethanol abuse on event-related potentials (ERPs) have demonstrated reduced P300 amplitudes in abstinent alcoholics (8,18,20,29-31). This finding does not change with prolonged abstinence (26) and was postulated to antecede the development of alcoholism. In 1984, Begleiter et al. (3) demonstrated reduced P300 in high risk vs. low risk individuals without the administration of ethanol. While the results of some subsequent studies have been either negative or equivocal (11,21,22,24), numerous studies have replicated this finding (4,5,10,14-16,27,28,39). It has been suggested that this P300 deficit antecedes the development of alcoholism and is a highly heritable trait, and may be considered as a biological phenotypic marker for the development of alcoholism (1,20).

Background

Since its discovery by Sutton et al. (1965) (35), the P300 component of the event related potential (ERP) has been

found to be associated with processes related to the updating of working memory (7), the information content of the stimulus (32) and factors related to the value or subjective significance of the stimulus (35), i.e., task relevance (36), unpredictability (6), infrequency (37), and motivational content (2).

There is evidence that P300 generation may reflect activation of both cortical and subcortical regions. Human studies, in which recordings from implanted electrodes were used to identify the neural generators of P300, have implicated medial temporal lobe structures, including the hippocampus and amygdala (9), the diencephalon (38), and cortical loci including frontal cortex and the inferior parietal lobule (34). On the basis of both intracranial recordings and lesion studies, Johnson (12,13) suggests that there may be different neural generators for both auditory and visual P300.

The present investigation assessed the consistency of the P300 component across six geographically separated laboratories, with each laboratory utilizing the same experimental design, stimulus presentation, and data acquisition hardware and software.

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METHODS

Subjects

The subjects in this study were 96, right-handed males ranging from 18 to 29 years of age ($\bar{X} = 22.1$). They constituted a national sample recruited by the six institutions comprising the COGA (Collaborative Study on the Genetics of Alcoholism) Project and are the basis for a series of interlaboratory ERP consistency studies. The participating laboratory locations included: Indiana University Medical School ($n = 16$, $\bar{X} = 22.9$), SUNY Health Science Center, Brooklyn ($n = 16$, $\bar{X} = 21.9$), University of California at San Diego ($n = 15$, $\bar{X} = 22.6$), University of Connecticut Health Center ($n = 17$, $\bar{X} = 20.4$), University of Iowa Health Center ($n = 17$, $\bar{X} = 21.9$), and Washington University School of Medicine ($n = 15$, $\bar{X} = 23.3$). The subject was required to be male, 18–29 years of age, in good health, not be taking any medication and have normal vision. He was given a questionnaire to assess the degree of drug and alcohol abuse as well as the medical and psychiatric history for both the subject and his first- and second-degree relatives. Positive findings in any of the aforementioned categories were cause for exclusion from the study. Furthermore, subjects were required to refrain from ingesting any alcoholic beverages for a minimum of 24 h before being tested. Verification was determined via a breathalyzer administered on the day of testing.

Experimental Design

The subject was seated comfortably in a dimly lighted, temperature regulated, sound-attenuated chamber; the same enclosure was used at each site (Industrial Acoustics Corp). Moreover, the same experimental procedure and stimulus presentation and data acquisition hardware and software were used at each lab. The subject was told to keep his eyes focused on a fixation target centrally displayed on a computer monitor (Concurrent Computer Corporation). Each subject wore a fitted electrode cap (Electro-Cap International, Inc.) containing the 21 leads of the 10/20 International System. The tip of the nose served as reference and the forehead as ground. Both vertical and horizontal eye movements were monitored. Artifact rejection (EOG, EMG and saturation artifact, $> 73.3 \mu\text{V}$) was performed on-line.

Electrical activity was amplified 10K (Sensorium EPA - 2 Electrophysiology Amplifiers) and recorded over a bandwidth of 0.02–50 Hz. Activity was sampled at a rate of 256 Hz, beginning 187 msec prior to stimulus onset and continuing for 1.62 s. After each stimulus presentation, all 21 channels of activity were simultaneously displayed on a monitor located outside the test chamber. Digital filtering (32 Hz low pass filter) of the raw data was performed off-line.

There were three classes of visual stimuli: target (the letter X), nontarget (squares), and novel (a set of completely different colored geometric figures and polygons that changed on each trial), with the following probabilities of occurrence: target (0.125), nontarget (0.75), and novel (0.125). Each stimulus subtended a visual angle of 2.5 degrees. Stimulus duration was 60 msec and the interstimulus interval (ISI) was 1.6 s. When the subject detected the target stimulus, he responded with the right index finger and depressed a button on a modified computer mouse as quickly as possible. Response speed was emphasized, but not at the cost of accuracy. The experiment terminated automatically after a minimum of 25 target stimuli, 150 nontarget stimuli, and 25 novel, artifact-free trials had been acquired. Trials with response times (RT) > 1000 msec

were rejected. The ERPs from accepted trials were automatically placed in target, novel, and nontarget response categories for subsequent summation, averaging, and statistical analysis. Differences in RTs to the target stimulus were also assessed across laboratories.

Data Analysis

For each subject, the average ERPs to the target, nontarget, and novel stimuli were analyzed via an automatic peak detection program. The P300 component was selected as the highest positive peak within a time window of 275–575 msec for the target, nontarget and novel stimuli. Thus, each subject's data consisted of peak voltages (μV) and latencies (msec) for each of the three stimulus conditions at each electrode. Statistical analyses included MANOVA, ANOVA and Sidak *t*-tests (33) and were used to determine whether statistical differences existed in P300 amplitudes and P300 latencies measured at the Pz electrode, for the target, nontarget, and novel stimuli at the six laboratories. P300 responses were analyzed at Pz because it is there that the responses are most robust, having their maximum amplitude. Additionally, there is substantial evidence indicating a significant reduction of P300 amplitude at the Pz electrode in both abstinent alcoholics (8,18–20,29,30–31) as well as high risk individuals (4,14,15,27,39).

RESULTS

Figure 1 presents the grand mean ($n = 96$) ERP waveform

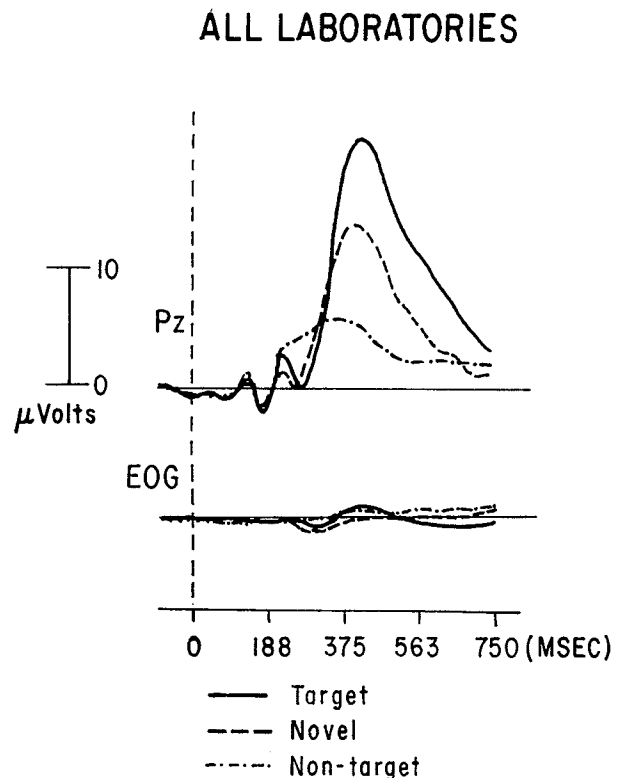


FIG. 1. The grand mean ERP waveform at the Pz electrode ($n = 96$) for the target, novel, and nontarget stimuli across all laboratories. Also presented are the grand mean vertical EOG waveforms.

at the Pz electrode to the target, novel, and nontarget stimuli. In a similar manner, Fig. 2 displays the grand mean ERP waveforms for each stimulus at each laboratory.

The results of the statistical analyses indicated that there were no statistically significant differences in any of the interlaboratory comparisons of P300 amplitude or latency at the Pz electrode. Individual MANOVAs were performed on P300 amplitude and P300 latency, under the target, nontarget and novel conditions across all six laboratories; neither result was statistically significant (P3 amplitude, $p > 0.38$; P3 latency, $p > 0.92$). Similarly, the results of the Sidak t -tests indicated no significant pairwise differences ($\alpha = 0.083$) for P300 amplitude or latency at Pz for any of the three stimulus conditions.

Separate ANOVAs for P300 amplitude and P300 latency were conducted for the target, nontarget, and novel conditions across laboratories. The results of these analyses confirmed those from the MANOVA and indicated no statistically significant differences in the P300 amplitude or P300 latency.

An ANOVA across laboratories was also performed on the RTs to the target stimulus. The grand mean RT was 449.9 msec, $SD = 57.7$, and there were no statistically significant differences in mean RT across laboratories ($p > 0.28$).

DISCUSSION

In the present investigation, a visual target selection paradigm was used to evaluate the consistency of the P300 response at the Pz electrode across six geographically separated laboratories. Each laboratory was required to use the same experimental procedure, hardware and software, to establish the generalizability of our findings across the six COGA locations. As a consequence, the results indicated no statistically significant differences in either P300 amplitude or latency for target, novel and nontarget stimuli at the Pz electrode across laboratories. We also observed that the novel response across laboratories had a Pz maximum, likely reflecting the effects of habituation.

The demonstration of a consistent interlaboratory P300 response at Pz suggests that P300 amplitude can now be pooled across these geographically separated locations and can be used in both segregation and linkage analyses assessing the familial transmission of alcoholism. Twin studies have documented a genetic contribution to P300 morphology (17, 23), while evidence that the P300 amplitude may be a potential marker for the development of alcoholism derives from investigations of individuals at high risk for the development of alco-

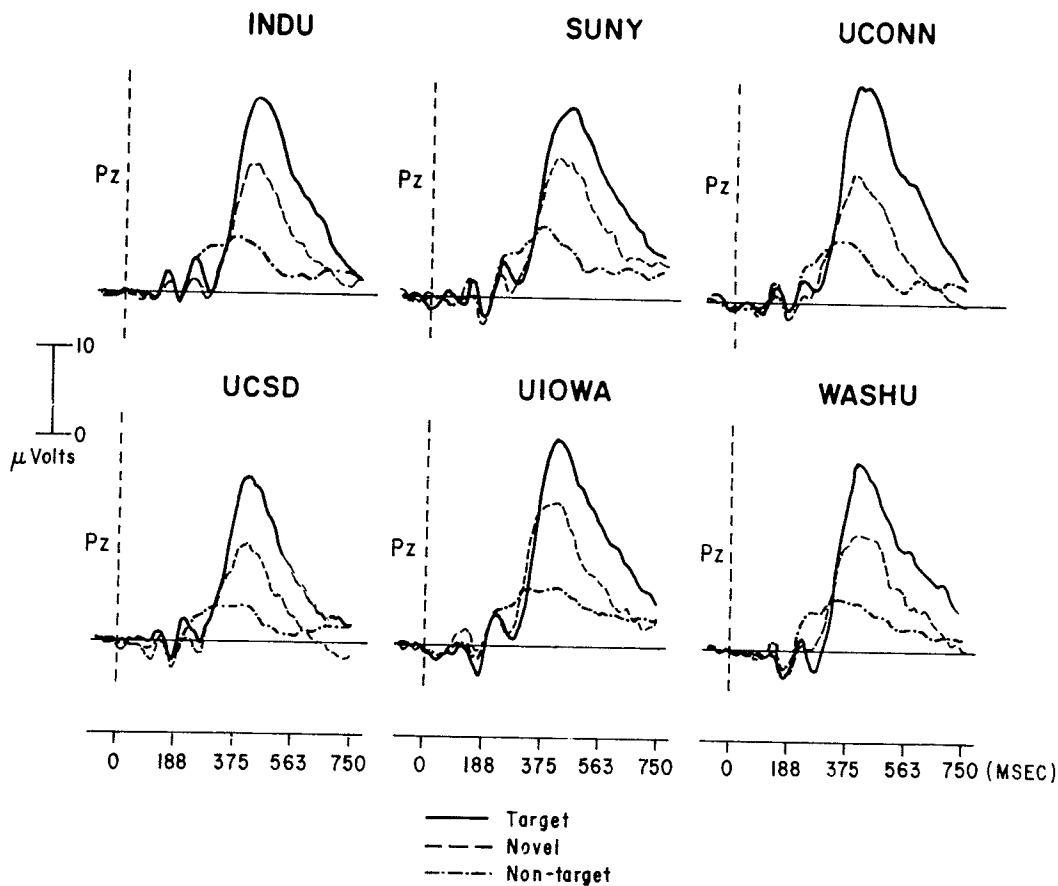


FIG. 2. Mean ERP waveform at the Pz electrode to the target, novel, and nontarget stimuli at each laboratory. INDU = Indiana University Medical School ($n = 16$); SUNY = State University of New York Health Science Center, Brooklyn ($n = 16$); UCONN = University of Connecticut Health Center ($n = 17$); UCSD = University of California at San Diego ($n = 15$); UIOWA = University of Iowa Health Center ($n = 17$); and WASHU = Washington University School of Medicine at St. Louis ($n = 15$).

holism who manifest reduced P300 amplitudes (3,4,14-16,27,39). It is interesting to note that in a recent meta-analysis of P300 amplitude from males at risk for alcoholism (25) the authors concluded that the P3 component, "may have predictive value as an index of vulnerability for alcoholism when well-designed paradigms are used to elicit ERPs."

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REFERENCES

- Begleiter, H.; Porjesz, B. Potential biological markers in individuals at high risk for developing alcoholism. *Alcohol. Clin. Exp. Res.* 12:488-493; 1988.
- Begleiter, H.; Porjesz, B.; Chou, C. L.; Aunon, J. P3 and stimulus incentive value. *Psychophysiology* 20:95-101; 1983.
- Begleiter, H.; Porjesz, B.; Bihari, B.; Kissin, B. Event-related brain potentials in boys at risk for alcoholism. *Science* 225:1493-1496; 1984.
- Begleiter, H.; Porjesz, B.; Rawlings, R.; Eckardt, M. Auditory recovery function and P3 in boys at high risk for alcoholism. *Alcohol* 4:314-321; 1987.
- Berman, S. M.; Whipple, S. C.; Fitch, R. J.; Noble, E. P. P3 in young boys as a predictor of adolescent substance use. *Alcohol* 10:69-76; 1993.
- Donchin, E.; Ritter, W.; McCallum, W. C. Cognitive Psychophysiology: The endogenous components of the ERP. In: Calloway, E. E.; Tueting, P.; Koslow, S. H., eds. *Event-related brain potentials in man*. New York: Academic Press; 1978:349-411.
- Donchin, E.; Karis, D.; Bashore, T. R.; Coles, M. G. H.; Gratton, G. Cognitive psychophysiology and human information processing. In: Coles, M. G. H.; Donchin, E.; Porges, S. W., eds. *Psychophysiology: Systems, processes and applications*. New York: The Guilford Press; 1986:244-267.
- Emmerson, R. Y.; Dustman, R. E.; Shearer, D. E.; Chamberlin, H. M. Visually evoked and event related potentials in young abstinent alcoholics. *Alcohol* 4:241-248; 1987.
- Halgren, E.; Squires, N. K.; Wilson, C. L.; Rohrbaugh, J. W.; Babb, T. L.; Crandall, P. H. Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. *Science* 210:803-805; 1980.
- Hill, S. Y.; Steinhauer, S. R. Assessment of prepubertal and postpubertal boys and girls at risk for developing alcoholism with P300 from a visual discrimination task. *J. Stud. Alcohol* 54:350-358; 1993.
- Hill, S. Y.; Steinhauer, S.; Park, J.; Zubin, J. Event-related potential characteristics in children of alcoholics from high density families. *Alcohol. Clin. Exp. Res.* 14:6-17; 1990.
- Johnson, R. Jr. Auditory and visual P300s in temporal lobectomy patients: evidence for modality-dependent generators. *Psychophysiology* 26:633-650; 1989.
- Johnson, R. Jr. On the neural generators of the P300 component of the event-related potential. *Psychophysiology* 30:90-97; 1993.
- Noble, E. P. Alcoholic fathers and their sons: Neuropsychological, electrophysiological, personality and family correlates. In: Cloninger, C. R.; Begleiter, H., eds. *Genetics and biology of alcoholism, Banbury report 33*. New York: Cold Springs Harbor Laboratory Press; 1990:159-174.
- O'Connor, S.; Hesselbrock, V.; Tasman, A. Correlates of increased risk for alcoholism in young men. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 10:211-218; 1986.
- O'Connor, S.; Hesselbrock, V.; Tasman, A.; DePalma, N. P3 amplitudes in two distinct tasks are decreased in young men with a history of paternal alcoholism. *Alcohol* 4:323-330; 1987.
- O'Connor, S. J.; Morzorati, S.; Christian, J. C.; Li, T.-K. Heritable features of the auditory oddball event-related potential: Peaks, latencies, morphology and topography. *Electroenceph. Clin. Neurophysiol.* 92:115-125; 1994.
- Patterson, B. W.; Williams, H. L.; Mclean, G. A.; Smith, L. T.; Schaffer, K. W. Alcoholism and family history of alcoholism: Effects on visual and auditory event-related potentials. *Alcohol* 4:265-274; 1987.
- Pfefferbaum, A.; Rosenbloom, M.; Ford, J. M. Late event-related potential changes in alcoholics. *Alcohol* 4:275-281; 1987.
- Pfefferbaum, A.; Ford, J. M.; White, P. M.; Mathalon, D. Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. *Alcohol. Clin. Exp. Res.* 5:839-850; 1991.
- Polich, J.; Bloom, F. E. P300 from normals and adult children of alcoholics. *Alcohol* 4:301-305; 1987.
- Polich, J.; Bloom, F. E. Event-related brain potentials in individuals at high and low risk for developing alcoholism. *Alcohol. Clin. Exp. Res.* 12:368-373; 1988.
- Polich, J.; Burns, T. P300 from identical twins. *Neuropsychologia* 25:299-304; 1987.
- Polich, J.; Haier, R.; Buchsbaum, M.; Bloom, F. E. Assessment of young men at risk for alcoholism with P300 from a visual discrimination task. *J. Stud. Alcohol* 49:186-190; 1988.
- Polich, J.; Pollock, V. E.; Bloom, F. E. Meta-analysis of P300 amplitude from males at risk for alcoholism. *Psych. Bull.* 115:55-73; 1994.
- Porjesz, B.; Begleiter, H. Human brain electrophysiology and alcoholism. In: Tarter, R. D.; Van Thiel, D., eds. *Alcohol and the brain*. New York: Plenum Press; 1985:139-182.
- Porjesz, B.; Begleiter, H. Event-related potentials in individuals at risk for alcoholism. *Alcohol* 7:465-469; 1990.
- Porjesz, B.; Begleiter, H. Neuropsychological factors associated with alcoholism. In: Hunt, W.; Nixon, S. J., eds. *Alcohol-induced brain damage*. NIAAA Research Monograph No. 22. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Institute on Alcohol Abuse and Alcoholism; 1993:89-120.
- Porjesz, B.; Begleiter, H.; Garozzo, R. Visual evoked potential correlates of information processing deficits in chronic alcoholics. In: Begleiter, H., ed. *Biological effects of alcohol*. New York: Plenum Press; 1980:603-623.
- Porjesz, B.; Begleiter, H.; Bihari, B.; Kissin, B. The N2 component of the event-related potential in abstinent alcoholics. *Electroenceph. Clin. Neurophysiol.* 66:121-131; 1987.
- Porjesz, B.; Begleiter, H.; Bihari, B.; Kissin, B. Event-related brain potentials to high incentive stimuli in abstinent alcoholics. *Alcohol* 4:283-287; 1987.
- Ruchkin, D.; Johnson, R.; Canoune, H.; Ritter, W. H.; Hammer, M. Multiple sources of P3b associated with different types of information. *Psychophysiology* 27:157-176; 1990.
- SAS/STAT User's Guide v. 6.03. Cary, NC: SAS Institute Inc.; 1988.
- Smith, M. E.; Halgren, E.; Sokolik, M.; Baudena, P.; Musolino, A.; Liegeois-Chauvel, C.; Chauvel, P. The intracranial topography of the P3 event-related potential elicited during auditory oddball. *Electroenceph. Clin. Neurophysiol.* 76:235-248; 1990.

35. Sutton, S.; Braren, M.; Zubin, J.; John, E. R. Evoked potential correlates of stimulus uncertainty. *Science* 150:1187-1188; 1965.
36. Sutton, S.; Tueting, P.; Zubin, J.; John, E. R. Information delivery and the sensory evoked potential. *Science* 155:1436-1439; 1967.
37. Tueting, P.; Sutton, S.; Zubin, J. Quantitative evoked potential correlates of the probability of events. *Psychophysiology* 7:385-394; 1971.
38. Velasco, M.; Velasco, F.; Velasco, A. L.; Almanza, X.; Olivera, A. Subcortical correlates of the P300 potential complex in man to auditory stimuli. *Electroenceph. Clin. Neurophysiol.* 64:199-210; 1986.
39. Whipple, S. C.; Parker, E. S.; Noble, E. P. An atypical neurocognitive profile in alcoholic fathers and their sons. *J. Stud. Alcohol* 49:240-244; 1988.