Increased Rate of P300 Latency Prolongation With Age in Schizophrenia: Electrophysiological Evidence for a Neurodegenerative Process

O’Donnell, Brian F. PhD; Faux, Steven F. PhD; McCarley, Robert W. MD; Kimble, Matthew O.; Salisbury, Dean F. PhD; Nestor, Paul G. PhD; Kikinis, Ron MD; Jolesz, Ferenc A. MD; Shenton, Martha E. PhD

From the Departments of Psychiatry (Drs O’Donnell, McCarley, Salisbury, Nestor, and Shenton and Mr Kimble) and Radiology (Drs Kikinis and Jolesz), Harvard Medical School, Boston, Mass; the Brockton (Mass) Veterans Affairs Medical Center (Drs O’Donnell, McCarley, Salisbury, Nestor, and Shenton and Mr Kimble); the Department of Radiology, Magnetic Resonance Imaging Division, Surgical Planning Center, Brigham and Women’s Hospital, Boston (Drs Kikinis and Jolesz); and the Department of Psychology, Drake University, Des Moines, Iowa (Dr Faux).

Outline

- Abstract
- RESULTS
  - GROUP DIFFERENCES
- AGE AND P300
- P300 AND CLINICAL STATUS
- AGING AND GRAY MATTER VOLUMES DETERMINED BY MRI
- COMMENT
- SUBJECTS AND METHODS
  - SUBJECTS
  - ERP EVALUATION
  - Recording Procedures
  - Data Processing
  - STATISTICAL ANALYSIS
- REFERENCES

Graphics

- Figure 1
Abstract

Background: The latency of the P300 event-related potential is prolonged in disorders associated with neural damage and degeneration and also becomes prolonged in the course of neural changes that accompany aging. We tested whether the rate of P300 latency increase with age was greater in male schizophrenic patients than in normal subjects because a steeper slope in schizophrenia would suggest a progressive neurodegenerative process. We also evaluated a subset of these subjects for changes in brain volumes as determined by magnetic resonance imaging.

Method: The P300 component was elicited during an auditory ‘‘oddball’’ paradigm and was recorded from 47 male patients with chronic schizophrenia whose mean age at onset was 22.4 years and from 47 age-, handedness-, and gender-matched control subjects. The relation of P300 latency and amplitude to age within each group was evaluated using correlation and regression analyses. Brain volumes determined via magnetic resonance imaging were evaluated by quantitative volumetric analyses of images acquired with three-dimensional Fourier transform and double echo-spin echo-pulse sequences.

Results: The slope of P300 latency on age was steeper for schizophrenic patients than for normal control subjects at midline frontal and central electrode sites. The slope of N100 latency did not differ, implying that the P300 differences were not likely to be due to peripheral hearing loss or damage affecting the initial stages of neural processing. Posterior superior temporal gyrus gray matter volume determined via magnetic resonance imaging significantly diminished with age on the left side in patients with schizophrenia but not on the right side or in controls; these slopes were not, however, statistically significantly different from each other.

Conclusions: These findings provide preliminary evidence that male patients with chronic schizophrenia experience a neurodegenerative process that becomes evident in adulthood and is reflected by the rate of change of P300 latency with age. Whether this process is due to the primary effects of schizophrenia or is secondary to factors associated with schizophrenia’s chronic course and treatment remains a question for future investigation.

(Arch Gen Psychiatry. 1995;52:544-549)

Since Kraepelin’s description of the course of schizophrenia sedementia praecox) at the beginning of the century,[1] the question of whether schizophrenia is a neurodegenerative disorder has elicited sustained interest and controversy. Although the long-term course of schizophrenia shows great heterogeneity among patients,[2-9] a significant number of patients, sometimes termed keraepelinian, experience very poor outcomes.[10,11] In particular, a subset of elderly patients institutionalized on a long-term basis shows severe cognitive impairment that is suggestive of a progressive neurodegenerative disorder and that is not associated with any known dementing illness.[5,12-20].

A major problem in evaluating the course of schizophrenia has been the lack of a noninvasive physiological marker for neurodegenerative changes in humans. One candidate marker is the P300 component of the event-related potential (ERP). This component is a large positive peak in the electroencephalogram about 300 to 500 milliseconds following the onset of task-relevant stimuli. In clinical studies, the P300 component is most commonly elicited using an ‘‘oddball’’ paradigm. In this paradigm, a subject is asked to count or respond to infrequent target stimuli that are randomly
interspersed among frequent nontarget stimuli; the target stimuli produce a large P300 response in normal subjects. Because P300 latency can be measured without requiring a behavioral response, it provides an index of information processing that is not affected by slowed or abnormal response production, as is the case with behavioral measures of function.

P300 latency is prolonged in adult-onset neurodegenerative disorders, including heterogeneous dementias,[21,22] Alzheimer’s dementia,[23] multiple sclerosis,[24] Huntington’s chorea,[25] Parkinson’s disease,[26,27] hydrogen sulfide intoxication,[28] and progressive supranuclear palsy.[29] P300 latency also becomes prolonged in the course of neural changes accompanying aging at a rate of 1 to 2 ms/y.[30-33] Consequently, if a sample of schizophrenic patients experienced a neurodegenerative process in adulthood, P300 latency would be likely to show an increased rate of prolongation (increased slope) with age. To test this hypothesis, we investigated the relation of auditory P300 latency to age in patients with chronic schizophrenia and in normal control subjects between 20 and 60 years of age.

RESULTS

GROUP DIFFERENCES

An analysis of variance on P300 latency at Fz, Cz, and Pz revealed a main effect of electrode site (F[2,184] equals 14.1, P less than .001), with earlier P300 latencies recorded at Fz than Pz in both groups, and no group or interaction effects. At Cz, control latency was 379 plus minus 32 milliseconds, and patient latency was 393 plus minus 52 milliseconds. An analysis of variance on P300 amplitude across electrode sites revealed a main effect for group (F[1,92] equals 36, P less than .001) and electrode site (F[2,184] equals 55.6, P less than .001). The SZ group had lower P300 amplitudes at all three sites, and P300 amplitude was largest at Pz and smallest at Fz. At Cz, control amplitude was 10.8 plus minus 4.7 mu V, and patient amplitude was 6.1 plus minus 4.0 mu V.

AGE AND P300

The slope of P300 latency on age was steeper in schizophrenic subjects, particularly at Fz and Cz. The slope of P300 latency on age at Fz was 0.65 ms/y (P equals .16) for control subjects and 2.98 ms/y (P equals .001) for schizophrenic subjects. At Cz, the slope was 1.21 ms/y (P equals .02) for control subjects and 3.18 ms/y (P less than .001) for schizophrenic subjects. The difference between slopes in the SZ and the NL groups was significant at both Fz (P equals .03) and Cz (P equals .04), using the t test for comparison of regression coefficients.[47] While the slope (b) of P300 latency on age at Pz was steeper in patients (b equals 2.11 ms/y, P equals .03) than in control subjects (b equals 1.54 ms/y, P equals .002), the difference between slopes was not statistically significant. The Figure showscatterplots, linear regression coefficients, and least square regression lines for P300 latency on age at Fz and Cz. P300 amplitude did not correlate with age at any site in either group.
It is possible that variations in experimental protocols across studies might affect the slope of P3 on aging. We compared slopes at $F_z$ separately for two samples evaluated before 1990 at this site [34,35] and for subjects evaluated since 1990 (NL group, 23 subjects; SZ group, 26 subjects). In the 1990 Faux et al study,[34] the interstimulus and baseline interval, high-pass setting, and artifact correction procedure differed slightly from more recent studies, as described in the ‘‘Subjects and Methods’’ section. In the 1993 Faux et al study,[35] patients were tested after they had stopped receiving medication and responded with a key press rather than a silent count. In each study, the slope of P300 on age was three to four times steeper in schizophrenic patients than in control subjects. For schizophrenic patients, the average slope of P300 latency on age was 3.2 ms/y (P equals .01 in Faux et al,[34] P equals .07 in Faux et al,[35] and P equals .02 in the new sample) in contrast to the mean control slope of 0.76 ms/y (P equals .25 in Faux et al,[34] P equals .32 in Faux et al,[35] and P equals .29 in the new sample).

We next tested whether the N100 component increased with age in schizophrenia. N100 latency is sensitive to conductive hearing loss or disturbances of neurotransmission within the peripheral auditory pathways but not to aging or dementia. The regression of N100 latency on age was not significant in either group at any of the three electrode sites.

**P300 AND CLINICAL STATUS**

---

**Figure 1.** Scatterplots and linear regression lines showing the relationship of P3 latency to age in both groups at $F_z$ and $C_z$. \( b \) indicates the slope.
One specific issue raised by the finding of an increased rate of P300 latency change in schizophrenic subjects is whether this could be attributed to differences in institutionalization, clinical status, or other patient characteristics. We thus evaluated the relation of P300 latency at Fz and Cz to the following variables: percentage of time hospitalized since onset, current chlorpromazine-equivalent dosage of neuroleptic medication, an estimate of lifetime dosage (current dosage multiplied by duration of illness), illness duration, age at illness onset, Mini-Mental State score, information subscale score from the WAIS-R and educational attainment.

P300 latency in outpatients did not differ from P300 latency recorded in inpatients. There was no correlation between an estimate of lifetime neuroleptic medication exposure and P300 latency. Current dosage and P300 latency were not correlated in medicated patients, but patients who were no longer receiving medication showed prolonged P300 latency compared with patients receiving medication at all three recording sites (Fz: P equals .002; Cz: P equals .004; Pz: P equals .03). P300 amplitude, in contrast to latency, did appear to be related to clinical status. P300 amplitude decreased with increased percentage of time hospitalized at Pz (r equals minus .42, P equals .01) and was also reduced in inpatients compared with outpatients at Cz and Pz (P less than .01 on t tests). Mini-Mental State score, the information subscale score from the WAIS-R, and educational attainment did not correlate with P300 latency or with amplitude.

Because current (testing) age equals age at illness onset plus illness duration, the latter two variables are, by definition, highly interrelated with age. In stepwise multiple regression analyses with P300 latency at Fz and Cz, with all three variables entered, current age was the only retained variable (P’s less than .01), with the contributions of onset age and duration being redundant (not significant). The colinearity (both duration and onset were significantly correlated with age, univariate P’s less than .005) and the limited range of the onset variable (all onsets at ages younger than 33 years) made valid multiple regression measurements of the relative strength of the contribution of these two variables not possible. For comparative purposes, we did perform stepwise multiple regression analyses that compared the effects of forced entry as the first variable, of duration of illness, and of age of onset. The mean percentages of variance explained (R^2) were similar (duration, 11.5%; onset, 11%); also, the mean absolute magnitudes of the univariate correlation coefficients were similar (vertical bar r vertical bar approximate equal .28) for duration and onset.

AGING AND GRAY MATTER VOLUMES DETERMINED BY MRI

In a subset of 15 schizophrenic patients who received MRI evaluations, we previously reported that reductions in gray matter volume of the left posterior superior temporal gyrus (STG) were correlated with P300 amplitude, particularly at electrode sites over the left temporal region.[37,48] In the original MRI study,[49] group differences had been tested using age as a covariate, with no change in the results, but the univariate relation of age to gray matter volumes was not explicitly evaluated. However, in view of these P300 findings, we examined whether aging had a differential impact on the absolute gray matter volume (in milliliters) of the left and right posterior STG in these 15 schizophrenic patients compared with 15 control subjects in the same study.

Posterior STG gray matter volume significantly diminished with age in the schizophrenic patients on the left side (r equals minus .61, b equals minus 0.07 mL/y, P equals .02) but not on the right side (r equals minus .39, b equals minus 0.05 mL/y, P equals .15). The difference between these correlation
coefficients and slopes in the SZ group was not significant. P300 latency in the SZ group did not correlate with left posterior STG volume in these patients. Control subjects showed no statistically significant decrease in posterior STG gray matter volume with age, either on the left side (r equals minus .20, b equals minus .02 mL/y, P equals .48) or on the right side (r equals minus .37, b equals minus 0.05 mL/y, P equals .17); these correlation coefficients and slopes were not significantly different from zero. In the SZ group, there was a trend for total brain gray matter volume to diminish with age (r equals minus .46, b equals minus 4.7 mL/y, P equals .08), but the NL group showed no such trend level significance (r equals minus .26, b equals minus 3.0 mL/y, P equals .35) in this relatively small sample; control-schizophrenic differences between slopes and correlation coefficients were not statistically significant.

COMMENT

The rate of increase of P300 latency with age in schizophrenic patients was greater than that in control subjects. These findings support the hypothesis that schizophrenia has a progressive course, at least in the subgroup of male patients with chronic schizophrenia who we studied. The slope of P300 latency on age in schizophrenic patients ranged from 2.1 to 3.2 ms/y across midline electrode sites, whereas in control subjects the range was 0.7 to 1.5 ms/y. This difference in slope was significant at Fz (P equals .03) and Cz (P equals .04). Because prolonged P300 latency has been demonstrated to be a reliable sign of a neurodegenerative process, this increased prolongation may be the first sign of a pathophysiological process that will later become manifest as a severe cognitive impairment [17,18] or as more severe negative symptoms and lack of independent living skills.[11] We note, however, that these findings of P300 prolongation and left posterior STG tissue reduction with advancing age may be characteristic of male patients with chronic schizophrenia, such as the sample reported herein, and not extend to other subgroups, such as female patients or patients with a less chronic course or a later age of onset. The great variability of P300 latency, even among older patients, suggests that a neurodegenerative process may be characteristic of only a subset of patients with chronic schizophrenia.

We tested whether the increased rate of change of P300 latency in schizophrenic patients might be explained by factors other than the schizophrenic process, such as the presence of a neurologic dementia, long exposure to an institutional environment, or other clinical status variables. None of the patients had a neurologic disorder, and all were below the usual age of onset for Alzheimer’s dementia. Furthermore, the absence of a relation between N100 latency changes with age implies that the P300 changes are not due to such factors as peripheral hearing loss or disturbances of the initial stages of neural processing because these would affect N100 [50] as well as P300. Also not correlated with P300 latency were percentage of time institutionalized since the first episode, mental status, educational attainment, and inpatient status. These findings suggest that institutionalization (as measured by percentage of time hospitalized) and current functional status (as indicated by outpatient vs inpatient status) did not account for variations in P300 latency with age. Patients who stopped receiving medication showed increased P300 latency relative to patients who continued to receive medication, suggesting that medication may tend to normalize P300 latency.[35] An estimate of lifetime neuroleptic medication exposure did not correlate with latency. Although subjects were screened to rule out addiction and recent substance abuse, the extent of any lifetime subaddictive use could not be ascertained from patient records. Although the current literature [51-54] does not indicate that nonaddictive lifetime use of alcohol or other substances influences P300 latency, we cannot exclude the possibility that nonaddictive use was greater in the patient than in the NL group and may have had an unknown degree of influence on P300 latency. We note also that the absence of correlation with the Mini-Mental State score and the information subscale score of the WAIS-R could reflect the constricted
range of scores in the group, which excluded patients with signs of dementia or other severe cognitive impairment.

We note that in the present cross-sectional sample, it was not possible to reliably disentangle the relative contributions of duration of illness and age of illness onset to the strong age-related correlations of P300 latency. Such a differentiation may be possible in the population of first-episode schizophrenic and age-matched control subjects [55] we are currently studying in the same P300 paradigm because we plan to do long-term, repeated follow-up measurements.

Gray matter volume of the left posterior STG, one probable determinant of the amplitude of the scalp-recorded auditory P300 component, showed an age-related decline that was significant in the SZ but not in the NL group. These MRI structural data are thus supportive of (although they do not prove) a neurodegenerative process and complement the functional P300 measures. That P300 latency in the SZ group did not correlate with left posterior STG volume (as did amplitude) suggests relatively independent effects of age on these two variables. It may be that latency would correlate more with white matter alterations, as it does in cases of neurotoxic effects and multiple sclerosis,[24] than with the changes in gray matter volumes measured in our MRI study. Focal and/or gross reduction of brain tissue in schizophrenic patients with age has also been reported in the literature. Testretest reduction of STG volume was noted by DeLisi and colleagues.[56] Less anatomically specific evidence of a neurodegenerative process, including decreased brain volume, decreased gray matter, increased ventricular size, or increased atrophy with age in schizophrenic subjects, have also been reported by some [57-60] but not all investigators.[61-63] It is consequently of interest that left posterior STG volume in our data showed a greater decline with age than did total gray matter. Although this difference did not attain statistical significance in this small sample, it is compatible with the possibility of regional brain differences.

Our data of increased rate of P300 latency prolongation in male patients with chronic schizophrenia is consistent with the presence of a neurodegenerative process. We caution, however, that there are methodologic limitations to the present study. First, longitudinal investigation of the same population, rather than the present cross-sectional sample, would provide a better design with respect to sampling and would also better be able to determine whether these findings reflect a primary effect of schizophrenia or conditions associated with this disorder, including administration of neuroleptic medication and other treatment. Second, the slope of P300 latency should also be studied in patients with a less chronic course, with well-characterized histories of alcohol or other substance use, and with detailed histories of lifetime neuroleptic medication use and in women because the presentation and course of schizophrenia differs between men and women.[64] Although our data do not provide firm proof of a neurodegenerative process, they should motivate further functional and structural studies of the neural consequences of aging in schizophrenia, particularly given the paucity of empirical data bearing on the question of the pathophysiological evolution of schizophrenia across the life span.

Accepted for publication January 20, 1995.

Supported by grants 40799 (Dr McCarley) and IR29 MH50747-01 (Dr Shenton) from the National Institute of Mental Health, Bethesda, Md, the Department of Veterans Affairs Medical Research Service and Schizophrenia Center, Brockton, Mass (Dr McCarley), the Commonwealth of Massachusetts Research Center, Boston (Dr McCarley), the National Alliance for Research on Schizophrenia and Depression (Chicago, Ill) Young Investigator Award (Dr O’Donnell), the National Institute of Mental Health Research Scientist Development Award K02-MH0110-01 (Dr Shenton), and the Stanley...
SUBJECTS AND METHODS
SUBJECTS

Forty-seven right-handed male schizophrenic patients between the ages of 20 and 60 years were recruited from the Brockton, Mass, and the Bronx, NY, Veterans Affairs Medical Centers. They were drawn from previously reported samples [34-37] and from a new series of evaluations. Seventeen were outpatients and 30 were inpatients at the time of testing. Twelve were not receiving medication at the time of testing; the remainder were receiving neuroleptic medication, with a mean plus minus SD daily dose equivalent to 576 plus minus 668 mg of chlorpromazine.[38] The DSM-III-R [39] diagnosis was ascertained on the basis of a structured psychiatric interview and the Schedule for Affective Disorders and Schizophrenia [40] and by a review of patients’ medical charts. Mean plus minus SD age at onset was 22.4 plus minus 4.0 years (range, 16 to 33 years), mean plus minus SD illness duration was 17.2 plus minus 7.4 years, and mean plus minus SD percentage of time hospitalized since first episode was 31.4% plus minus 25.0%. None of the subjects had a history of electroconvulsive shock treatment, alcohol or other drug abuse (DSM-III-R criteria) within the last 5 years, addiction, or a neurologic illness affecting the central nervous system.

The normal control group (NL group) included 47 age-, handedness-, and gender-matched subjects who were recruited from newspaper advertisements. Information obtained from structured interviews were used to exclude control subjects if they had a history of alcohol or other drug abuse, psychiatric or neurologic illness, or psychiatric illness in a first-degree relative.

The NL group did not differ from patients with schizophrenia (SZ group) in mean plus minus SD age (NL group, 39.6 plus minus 9.1 years; SZ group, 39.5 plus minus 8.0 years). Although none of the schizophrenic patients was demented at the time of testing, patients had slightly worse (P equals .009) mean plus minus SD Mini-Mental State scores (NL group, 28.9 plus minus 1.5; SZ group, 27.6 plus minus 3.0)[41] and Wechsler Adult Intelligence Scale-Revised (WAIS-R) information subscale scores (NL group, 11.4 plus minus 2.5; SZ group, 9.8 plus minus 2.7).[42]

ERP EVALUATION
Recording Procedures

The ERPs were recorded using an auditory oddball paradigm. Infrequent (P equals .15) target tones (1500 Hz, 97-dB sound pressure level) were presented among frequent nontarget tones of a lower pitch (1000 Hz, 97-dB sound pressure level). Tone pips were of 40 milliseconds’ duration and presented with a 1.2-second interstimulus interval through insert earphones (Neuroscan, Herndon, Va) against a background of continuous 70-dB binaural white noise. Three blocks of 200 tones were presented. Subjects silently counted the tones (NL group, 36 patients; SZ group, 35 patients) or responded to target tones with a button press (NL group, 11 patients; SZ group, 12 patients). While listening to the tones, subjects stared at a central fixation point to reduce eye movements. The ERPs were recorded from 28 tin plate scalp electrodes using an electrode cap (Electro-Cap International Inc, Dallas, Tex) referenced to linked ear electrodes. Scalp electrode placements included 20 electrodes in the International 10-20...
system [43] with eight additional interpolated electrodes. A vertical electro-oculogram (EOG) was recorded using right eye supraorbital and infraorbital electrodes. A horizontal EOG was recorded from electrodes at the right and left external canthi. Electrode impedance was maintained at less than 4 k Omega. Right and left ear impedances were matched within 1 k Omega. The electroencephalogram was filtered using a bandpass of 0.15 to 40 Hz, with 36 dB per octave roll-off for low pass and 6 dB per octave roll-off for high pass. Single trial epochs were digitized and stored on hard disk for later off-line processing. Each ERP consisted of 256 electroencephalogram samples over a 700-millisecond epoch, including a 100-millisecond prestimulus baseline interval.

Thirteen control subjects and 10 patients from the sample described in Faux et al [34] received an ERP protocol that differed from that described above in the following ways: the interstimulus interval was 1.0 second, the baseline interval was 16 milliseconds, the high-pass filter cutoff was 0.3, and on-line vertical EOG artifact rejection was used.

Data Processing

All single-trial epochs were baseline corrected prior to subsequent processing. The ERP responses with vertical EOG artifact were corrected using individually computed weighting coefficients at each electrode site using the procedure of Semlitsch et al.[44] After correction for vertical EOG artifact, all epochs with voltages in excess of plus minus 50 mu V at any site were rejected. Epochs were then sorted into infrequent target ERP and frequent nontarget ERP averages. Each averaged ERP was then digitally low-pass filtered at 16 Hz to attenuate high-frequency electromyographic artifact.

P300 latency and amplitude were measured at F z , C z , and P z as the most positive voltage sampled in the latency range of 300 to 500 milliseconds. P300 most commonly has been evaluated at these sites in ERP studies of aging, and the component is largest at midline sites. Because P300 latency might be delayed by peripheral factors such as conductive hearing loss or alterations in subcortical neurotransmission, we also measured the N100 component, which precedes the P300 component in the waveform. Unlike P300, N100 latency is usually unaffected by age or dementia.[45,46]

STATISTICAL ANALYSIS

Mixed-model analyses of variance were used to compare latency and amplitude values of the P300 component between groups among midline sites (F z , C z , and P z ). Linear regression coefficients were computed to determine the slope of component latency on age. The percentage of variance explained was not increased using logarithmic or quadratic regression, and linear regression was thus selected as the simplest model. In the SZ group, the relation between measures of clinical status and ERP component values were evaluated using Pearson correlation coefficients or independent t tests. All P values reported are two tailed. Data are presented as mean plus minus SD.

REFERENCES


5. Ciompi L. Catamnestic long-term study on the course of life and aging of schizophrenics. Schizophr Bull. 1980;6:606-618. [Medline Link] [PsycINFO Link] [Context Link]


7. Harding CM, Brooks WW, Ashikaga T, Strauss JS, Breier A. The Vermont longitudinal study of persons with severe mental illness, II. Am J Psychiatry. 1987;144:727-735. [Medline Link] [PsycINFO Link] [Context Link]


11. Keefe RSE, Lobel DS, Mohs RC, Silverman JM, Harvey PD, Davidson M, Losonczy M, Davis KL. Diagnostic issues in chronic schizophrenia. Schizophr Res. 1991;4:71-79. [Medline Link] [PsycINFO Link] [Context Link]

12. Angst J. European long-term follow-up studies of schizophrenia. Schizophr Bull. 1988;14:501-513. [Medline Link] [PsycINFO Link] [Context Link]

13. Casanova MF, Carosella NW, Gold JM, Kleinman JE, Weinberger DR, Powers RE. A topographical study of senile plaques and neurofibrillary tangles in the hippocampi of patients with Alzheimer’s disease and cognitively impaired patients with schizophrenia. Psychiatry Res. 1993;49:41-62. [Medline Link] [PsycINFO Link] [BIOSIS Previews Link] [Context Link]


16. Johnstone EC, Cunningham DG, Gold A, Crow TJ, Macmillan JF. Institutionalization and the
defects of schizophrenia. Br J Psychiatry. 1981;139:195-203. [Medline Link] [PsycINFO Link] [Context Link]

17. Liddle PF, Crow TJ. Age disorientation in chronic schizophrenia is associated with global intellectual impairment. Br J Psychiatry. 1984;144:193-195. [Medline Link] [PsycINFO Link] [Context Link]


22. Pfefferbaum A, Wenegrat BG, Ford JM, Roth WT, Kopell BS. Clinical application of the P3 component of the event-related potentials, II: dementia, depression and schizophrenia. Electroencephalogr Clin Neurophysiol. 1984;59:104-124. [Medline Link] [PsycINFO Link] [Context Link]


29. Pierrot-Deseilligny C, Turell E, Penet C, Lebrigand D, Pillon B, Chain F, Agid Y. Increased wave
P300 latency in progressive supranuclear palsy. J Neurol Neurosurg Psychiatry. 1989;52:656-658. [Context Link]


34. Faux SF, Shenton ME, McCarley RW, Nestor PG, Marcy B, Ludwig A. Preservation of P300 event-related potential topographic asymmetries in schizophrenia with use of either linked-ear or nose reference sites. Electroencephalogr Clin Neurophysiol. 1990;75:378-391. [Medline Link] [PsycINFO Link] [Context Link]

35. Faux SF, McCarley RW, Nestor PG, Shenton ME, Pollak SD, Penhune V, Mondrow E, Marcy B, Peterson A, Horvath T, Davis KL. P300 topographic asymmetries are present in unmedicated schizophrenics. Electroencephalogr Clin Neurophysiol. 1993;88:32-41. [Medline Link] [PsycINFO Link] [BIOSIS Previews Link] [Context Link]


37. McCarley RW, Shenton ME, O'Donnell BF, Faux SF, Kikinis R, Nestor PG, Jolesz FA. Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. Arch Gen Psychiatry. 1993;50:190-197. [Fulltext Link] [Medline Link] [PsycINFO Link] [BIOSIS Previews Link] [Context Link]


41. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State. J Psychiatr Res. 1975;12:189-198. [Medline Link] [PsycINFO Link] [Context Link]


44. Semlitsch HV, Anderer P, Schuster P, Presslich O. A solution for reliable and valid reduction of ocular artifacts applied to the P300 ERP. Psychophysiology. 1986;23:695-703. [Medline Link] [PsycINFO Link] [Context Link]

45. Iragui VJ, Kutas M, Mitchiner MR, Hillyard SA. Effects of aging on eventrelated potentials and reaction times in an auditory oddball task. Psychophysiology. 1993;30:10-22. [Medline Link] [BIOSIS Previews Link] [Context Link]


51. Patterson WP, Williams HL, McLean GA, Smith LT, Schaeffer KW. Alcoholism and family history of alcoholism. Alcohol. 1987;4:265-274. [Medline Link] [PsycINFO Link] [Context Link]


53. Polich J, Bloom FE. P300 from normals and adult children of alcoholics. Alcohol. 1987;4:301-305. [Medline Link] [PsycINFO Link] [Context Link]

54. Steinhauer SR, Hill SY. Auditory event-related potentials in children at high risk for alcoholism. J Stud Alcohol. 1993;54:408-421. [Medline Link] [PsycINFO Link] [BIOSIS Previews Link] [Context Link]


58. Nasrallah HA. Progressive and static ventriculomegaly in schizophrenia: clinical and methodological variables. Schizophr Res. 1991;5:191-192. [Medline Link] [Context Link]

59. Waddington JL, O’Callaghan E, Buckley P, Larkin C, Redmond O, Stack J, Ennis JT. The age dependencies of MRI abnormalities in schizophrenia suggest early ventricular enlargement but later prominence of cortical atrophy. Schizophr Res. 1991;5:188-189. [Medline Link] [Context Link]

60. Woods BT, Yurgelin-Todd D. Brain volume loss in schizophrenia: when does it occur and is it progressive? Schizophr Res. 1991;5:202-203. [Medline Link] [Context Link]

61. Goldberg TE, Hyde TM, Kleinman JE, Weinberger DR. Course of schizophrenia. Schizophr Bull. 1993;19:797-804. [Medline Link] [PsycINFO Link] [BIOSIS Previews Link] [Context Link]

62. Vita A. Cerebral ventricular abnormalities in schizophrenia: evidence of their early origin and stability over time. Schizophr Res. 1991;5:189-190. [Medline Link] [Context Link]

63. Andreasen NC, Swayze VW, Flaum M, Yates WR, Arndt S, McChesney C. Ventricular enlargement in schizophrenia evaluated with computed tomographic scanning. Arch Gen Psychiatry. 1990;47:1008-1015. [Medline Link] [PsycINFO Link] [Context Link]

64. Goldstein JM, Tsuang MT. Gender and schizophrenia: an introduction and synthesis of findings. Schizophr Bull. 1990;16:179-183. [Medline Link] [PsycINFO Link] [Context Link]