Event-related potentials in schizophrenia: their biological and clinical correlates and a new model of schizophrenic pathophysiology*

Robert W. McCarley, Steven F. Faux, Martha E. Shenton, Paul G. Nestor and Jane Adams

Harvard Medical School, Department of Psychiatry, Brockton VAMC and Massachusetts Mental Health Center

(Received 19 February 1990, accepted 27 February 1990)

Evidence is growing that schizophrenic patients show significant structural damage in the temporal lobe limbic system. We review event-related potentials abnormalities (ERPs) in schizophrenia that may be related to dysfunction in this brain region or its inputs; ERPs discussed include the N100/P200, P300 and N400 components. Additional CT and clinical data have led our laboratory to a unifying working hypothesis of the presence of temporal lobe damage in schizophrenics that is evinced electrophysiologically as ERP alterations, structurally as tissue loss/derangement, and clinically as positive symptoms. The final section of this paper presents a new model of at least one form of schizophrenic pathology that, while speculative, incorporates experimentally based data from both our ERP work and from basic cellular physiology and pharmacology. The model proposes that positive symptoms of schizophrenia are related to limbic system pathology and in particular to a dysregulation of the NMDA form of excitatory amino acid transmission, potentiated by stress, and leading to cell damage and death due to ‘excitotoxicity’.

Key words: Event-related potential; P300; N400; Excitotoxicity; Excitatory amino acid; (Schizophrenia)

INTRODUCTION

ERPs are averaged, time-locked segments of EEG that follow the presentation of a stimulus, whose sensory modality may be visual, auditory or somatic. The ERPs are to be distinguished from the EEG, which represents a continuous, non-averaged record of brain potentials. Computerized signal averaging has led to a routinely excellent resolution of the small brain signals that are ERPs (4–15 μV). The ERP signals are derived from synchronous electrical activity in large populations of neurons. The activity that is summated is primarily the post-synaptic potentials representing increased or lessened polarization of the neuronal membrane, and detectable at scalp electrodes because of similar spatial orientation of the neuronal generators. ERPs may be divided into short-latency and long-latency portions or components. The very short-latency auditory ERP components, up to about 20 ms latency, are known to represent the various steps in propagation of brain activity along fiber tracts and the relay nuclei to cortex**. These very early brainstem components of the

** These very early brainstem components are derived from synchronous volleys of action potentials, and are the exception to the rule that ERPs are not derived from action potentials. Action potentials, in general, are not detectable because they are too brief and asynchronous, and also do not usually occur in neuronal somata/dendrites or fibers having the same spatial orientation.
auditory ERP are relatively constant in waveform shape across most forms of cognitive processing. In contrast, the longer latency ERP components, those with a latency of 100 ms and more, show a great influence of cognitive processing on waveform shape and even presence, and it is these ERPs that we shall discuss in this article. In these long latency ERPs the same physical stimulus presented under different conditions of cognitive processing may exhibit large differences in waveform shape. These differences index various aspects of cognitive processing and are thus of great interest to the cognitive neuroscientist, neurologist and psychiatrist.

ERPs are labeled by a shorthand notation which describes polarity — P for positive or N for negative — and the latency in milliseconds, the time of occurrence after stimulus onset. Thus N100 is a negative peak that occurs approximately 100 ms after a stimulus and P300 is a positive peak that occurs approximately 300 ms after the presentation of a stimulus. Fig. 1 illustrates those components of the ERP that have been utilized by our laboratory in the study of schizophrenia and that are discussed in this chapter: the N100, P200, P300 and N400. For simplicity, the word 'component' is often omitted in description of ERPs, and we and the literature often say 'P300 ERP' for 'P300 component of the ERP'.

The waveform in the first row of Fig. 1 is an auditory ERP produced by a tone pip, attended to by subjects, but without instructions to produce a covert or overt response to it. The most prominent components in this auditory ERP are the N100 and P200. These are obligatory potentials in the sense that they would be produced regardless of whether

![Waveform diagram](image)

Fig. 1. Example waveforms of various event-related potentials, and suspected to have sources in temporal lobes. Specific stimuli eliciting each waveform and specific temporal lobe sources are also identified. Row 1: the N100/P200 waveform, elicited by a simple tone pip, occurs automatically without cognitive processing. Row 2: the P300 waveform only occurs when subjects attend to rare meaningful stimulus events. Row 3: the N400 waveform is related to language processing and occurs when subjects process words which have an unexpected context.
the tone was attended or ignored, although the amplitude of the waveform may be modulated by cognitive processing. The second waveform (P300, row 2) resulted from a similar auditory stimulus, but this time the subjects were asked to count silently the rare (15%), high-pitched tones embedded among more frequent low-pitched tones. Here, the nature of the task and the cognitive processing, but not the physical stimulus, produced a large P300 response. Note the absence of a P300 in the row 1 waveform, and also the presence of the obligatory N100-P200 potentials in the row 2 waveform. The P300 occurs when an unusual stimulus is processed, e.g., counted. In fact the P300 waveform is most likely produced by processes quite separate from the physical stimulus itself, since a P300 waveform is associated with even an ‘omitted stimulus’, i.e., a gap in an otherwise regular series of tones. The third waveform (row 3), the N400, is also the result of cognitive processing, but this time the eliciting stimuli were verbal. In this task, subjects are asked to discriminate between sentences with unexpected or expected word endings, such as ‘Mary had a little APPLE’ versus the more expected ‘Mary had a little LAMB’. The main point is that the existence of different kinds of cognitive (brain) processing can be demonstrated using ERP techniques, even when subjects are not producing any overt motor response. Our work has been to determine whether these ERP waveforms are useful for understanding how brain functions may differ between psychopathological and normal populations. The reader will note that the great advantage of ERPs over the spontaneous, continuous EEG is that the stimuli leading to the brain potentials in ERPs are external, defined and thus capable of being brought under experimental control, whereas much uncertainty exists over the internal processing generating the spontaneous EEG.

ADVANTAGES AND DISADVANTAGES OF ERPS AS A WINDOW ON BRAIN ACTIVITY IN SCHIZOPHRENIA

The technique of scalp-recorded event-related potentials appears to have special advantages for the study of brain function in that: (1) the time resolution is in the millisecond range and thus more than a 1000-fold more rapid than PET, SPECT, and xenon brain imaging techniques; (2) scalp-recorded ERPs are ‘non-invasive’, non-hazardous, and may hence be repeated as often as desired; (3) they are relatively inexpensive to obtain; (4) their fine-grained time resolution, essentially at the speed of thought and cognitive processing, readily adapts ERPs to coupling with particular cognitive tasks. These tasks may then be tailored to reveal aspects of functional deficits in schizophrenia, as shown in the ERPs discussed in this review; (5) ERPs are related to specific aspects of cognitive processing, in contrast to autonomic variables such as heart rate and blood pressure, which appear principally to index the degree of effort in the tasks used to elicit ERPs (e.g., Veltman et al., 1989).

ERPs’ principal disadvantage is that, in marked contrast to electrophysiological work at the cellular level, they alone do not provide unequivocal information on the localization of their brain sources. This is because the voltages in ERPs are generated by current flow that travels not only through brain but also through scalp, bone and meninges, structures that do not provide a uniform resistance and thus may distort the apparent site of origin. We hasten to add that we do not mean to suggest that ERPs are without source information at all. As will be illustrated below, they may be combined with information from other techniques to allow solid inferences about sources. To further allow for inferences about source, we have emphasised the use of arrays of multiple scalp electrode to allow measurement of voltage distribution on the scalp, the voltage topography. Topography is an important variable because (1) potentials which differ in topography cannot come from identical dipole sources; and (2) recent developments in dipole modelling of source potentials (based on scalp potentials from large electrode arrays), although not providing mathematically unique solutions, can often account for 99% of waveform variability with 2-4 dipole solutions (Scherg and Von Cramon, 1985, 1986, 1990; Scherg, 1989). We generically refer to such topographic studies as brain potential imaging or BPI studies.

Within schizophrenia research, we view ERPs as especially useful in effecting links between the different research domains of brain/structural pathology (post-mortem and CT/MRI tech-
niques), cognitive characteristics and clinical pathological symptoms, and thereby helping to provide a unified picture of brain/cognitive functioning in major mental illness. Our focus has been primarily on schizophrenia, now generally recognized to result from brain pathology. For example, our ERP data have led us to a unifying working hypothesis relating these domains:

*There is temporal lobe damage in schizophrenics that is evinced electrophysiologically as ERP alterations, structurally as tissue loss/derangement, and clinically as positive symptoms.*

Positive symptoms are the hallucinations, delusions, and thought disorder characteristic of schizophrenia, and are to be contrasted with the negative symptoms of schizophrenia, such as poor self care, poverty of speech, blunted affect, etc. Our strategy is to maximize these links by selecting ERPs that are (a) cognitively meaningful as shown by links to a specific cognitive task in normals, and (b) likely to provide information on disturbed function in schizophrenia, because of the ERPs' relationship to clinical symptoms or other pathology. We then attempt to associate any ERP abnormalities with brain sources through information based on our own or others' data on structural, depth recording or neuropathological findings in schizophrenia. The ERPs and cognitive processes that are of special interest for this approach are surveyed below.

**N100 AND P200 ERP COMPONENTS**

The auditory N100 and P200 components are interrelated negative and positive ERPs, which peak about 100 and 200 ms after the presentation of a discrete auditory stimulus, such as a tone pip (see Fig. 1). N100 and P200 components are concentrically distributed with amplitude maxima at frontocentral and central sites, respectively (e.g., Vaughan et al., 1970; Picton and Hillyard, 1974; Simpson et al., 1977; Picton et al., 1978; Vaughan et al., 1980; Wood and Wolpaw, 1982). Although these potentials are automatically produced, functionally they appear to be related to early stimulus encoding at the auditory cortex (e.g., Picton and Hillyard, 1974; for review see Naatanen and Picton, 1987). It is clear, however, that these waves do not represent a single neurophysiological or psychological process, and that these waves are a composite of multiple coactive generators (Naatanen and Picton, 1987). The major source contributor appears to be auditory temporal cortex (Scherg and Von Cramon, 1985, 1986, 1990; Scherg, 1989), but inferior parietal (Knight et al., 1987) and frontal regions (Naatanen and Picton, 1987) may be involved as well. Unilateral lesions of temporal lobe have been reported to produce both symmetrical and asymmetrical amplitude deficits (Perronnet and Michel, 1977; Knight et al., 1980, 1987; Wood et al., 1984; Scherg and Von Cramon, 1985, 1986, 1990; Scherg, 1989). Scherg and Von Cramon (1990) also have shown that near-symmetrical amplitudes sometimes found in unilateral lesioned patients are best explained by a single temporal dipole location in the intact hemisphere.

Since the auditory N100-P200 components have been associated with early stimulus processing and temporal lobe generators, these components may be especially relevant to the study of schizophrenia, which has been similarly linked to deficits in stimulus processing (cf. Baribeau-Braun et al., 1983) and to temporal lobe pathology (see discussion below in P300 section). Indeed, a large number of studies and paradigms (usually limited to central electrodes) have reported an amplitude decrement of the auditory N100 and P200 components in schizophrenia compared to normal controls (e.g., Jones and Callaway, 1970; Saletu et al., 1971; Roth and Cannon, 1972; Cohen, 1973; Shagass et al., 1977, 1982; Lifshitz et al., 1979; Roth et al., 1979, 1980; Adler et al., 1982). These findings have been replicated numerous times in both medicated and unmedicated patients, although recent reports seem to indicate that benzodiazepines may additionally reduce N100-P200 amplitudes (Pfefferbaum et al., 1989).

Data from our laboratory illustrate the magnitude of these reductions in both medicated and unmedicated patients. Fig. 2 shows grand-averaged N100-P200 waveforms for both schizophrenics and normal controls. Fig. 3 shows that N100-P200 amplitude reductions exist over widespread portions of the scalp from left to right (MANOVA also reveals overall amplitude reduction, $P<0.05$). In this case the data were scored adjusting for the peak latency of each electrode site. These data are not related to hearing diffi-
Fig. 2. Schizophrenic versus normal control group amplitude differences on P200 are present in both a linked ears and a nose reference electrode recording condition. Illustrated are grand-averaged waveforms at T3, Cz, and T4 for the ERP elicited by the non-target stimulus in the counting condition. The time period of comparison, 204–272 ms, was that used on our previous study (Shenton et al., 1990) and encompasses the peak and period of steepest decline of the P200. Hotelling’s $T^2$ analysis of P200 integrated amplitudes on this time period showed large overall normal control > schizophrenic group amplitude differences in both the linked ears reference condition ($F (5, 34) = 3.74, P < 0.05$) and in the nose reference condition ($F (5, 34) = 4.10, P < 0.05$). These data confirm our previous findings in medicated schizophrenics (Shenton et al., 1989), and indicate that linked ears and nose references give approximately equal performance for the P200 differences. The normal controls and medicated schizophrenic subjects and recording conditions are described in Faux et al. (1990).

culty, since the patients demonstrate normal hearing. Scherg and Von Cramon (1985, 1986, 1990) and others (reviewed in Wood et al., 1984) have shown similar amplitude reductions in patients with unilateral lesions of auditory temporal cortex. The role of temporal lobe is not entirely clear, however. For example, Knight et al. (1987) have shown abolished P200 responses in patients with inferior parietal lobe lesions, but not with superior temporal gyrus (STG) lesions. These data probably mean, however, that several regions are essential for P200 generation, even if the major contributing source is the neocortex of temporal lobe.

Our laboratory has also reported results of the descending phase of the P200 (peak to baseline), where we have found large amplitude deficits in schizophrenics in the left temporo-central scalp regions. These electrophysiological abnormalities appear to be correlated with negative symptoms (Shenton et al., 1989a). Chronic medicated schizophrenics ($n = 11$) showed a diminished amplitude of the peak to baseline of the P200 component compared with normals. Topographically this feature was most prominent centrally (Cz), with a slight left temporal bias. The P200 waveform associated with the experimental condition of
counting infrequent stimuli ('infrequent attentive experimental condition') showed a high level of correlation with the total score and five subscales of the Scale for Assessment of Negative Symptoms (SANS) (see Andreasen, 1981), with the 'Total Score' having a Spearman's $\rho$ equal to 0.64 (correlations were highest at the Cz and C3 electrodes). In contrast, correlations with the Scale for the Assessment of Positive Symptoms (SAPS) (see Andreasen, 1984) and the Thought Disorder Index (TDI) (see Johnson and Holtzman, 1979) were minimal. Interestingly, only the 'attentional impairment' subscale of SANS did not show statistically significant correlations. These correlations may actually support the validity of the negative-positive symptom dichotomy, since attentional deficits are considered by many to be a positive symptom. Another important feature of the P200 peak to baseline amplitude was the absence of correlation with P300 component amplitude (300–400 ms, discussed below) at either T3 or Cz electrode sites, and thus indicating that these two ERPs may be useful probe pairs in investigations of schizophrenia. We have just begun to analyze new P200 data from new groups of medicated and unmedicated groups of schizophrenics. Data from the medicated schizophrenic group ($n=20$). These grand-averaged waveform data are displayed in Fig. 3, and a multivariate analysis confirmed schizophrenic/normal control differences on 204–272 ms integrated amplitude of the same coronal band of electrodes (T3, C3, Cz, C4, T4) as Shenton et al. (1989a).

As alluded to above, even if temporal cortex is the primary source generator of the N100-P200 complex, other brain regions may modulate these components (e.g., as a function of subject cognitive set). For example, the cerebral blood flow studies of Roland and coworkers (1985a, 1985b) suggest that frontal cortex plays an important role in modulating the activity in other sensory cortical regions, including the temporal-parietal regions implicated in the generation of N100-P200. In our schizophrenic patients we have shown (McCarley et al., 1989) that signs of frontal lobe tissue loss (frontal sulcal and anterior fissure enlargement) were highly correlated with P200 amplitude in attentive but not in other experimental conditions. Because of the possible frontal lobe-P200 modulation and the postulated link between negative symptoms and frontal abnormalities in schizophrenia (Shelton and Weinberger, 1986; Weinberger, 1986) it is not too surprising that there may also be a link between P200 amplitude and negative symptoms. Another important source of modulation may be inferior parietal lobe, as shown in lesion studies (Knight et al., 1987).
P300 ERP STUDIES

The auditory P300 component (See Fig. 1) of the ERP occurs when subjects detect and process infrequent and meaningful changes in the auditory environment. This positive-going potential typically occurs between 300 and 400 ms after the presentation of a task-relevant, infrequent auditory stimulus. It is of maximal amplitude over the midline at central and parietal scalp sites, and it is thought to originate, at least partly, from temporal lobe generators. Particularly hippocampus (reviewed in McCarley et al., 1989) and recordings at lateral scalp electrodes over the temporal lobe appear to be most sensitive to alterations in the temporal lobe component of the P300, as studied in patients with temporal lobe tissue loss associated with epilepsy (McCarthy et al., 1989; Wood et al., 1989).

Several lines of experimental literature have associated the P300 latency of normal volunteers with the chronometry of information processing (e.g., Kutas et al., 1977; Donchin et al., 1978; McCarthy et al., 1981; Ford et al., 1982; Polich et al., 1983). For example P300 latency is increased by increased demands for detection and categorization of stimuli. Similarly, P300 amplitude has been associated with the probability of occurrence, task relevance, subjective probability, decision confidence, equivocation, resolution of uncertainty, and stimulus incentive value (for an excellent review see Johnson, 1986). Donchin (1979) has conceptualized the P300 as the physiological correlate of updating of a cognitive hypothesis, i.e., updating what is expected in the environment. Posner (1975) has further related the P300 to channel-limited information processing, i.e., the P300 may reflect allocation of cognitive resources.

Because veridical cognitive updating and information processing may be a primary deficit in schizophrenia, it is not surprising that the P300 component of the ERP has attracted interest in schizophrenia studies. Extensive parametric studies in normals have shown that the P300 amplitude at a few (1–4) midline electrode sites (usually Cz and Pz) is inversely related to subjective estimation of stimulus probability and directly related to task relevance (see review in Donchin, 1979). In addition, numerous studies utilizing similar electrode sites and an ‘oddball task’ (detecting and processing the presence of an unusual stimulus) have shown that a decrement in auditory P300 amplitude in schizophrenia is a robust finding, being present in 19/23 studies reviewed by Roth et al. (1986; see also, Pritchard, 1986). Our laboratory’s use of a full set of International 10–20 electrodes demonstrated that schizophrenic-normal control differences were most pronounced in the left temporal region, where schizophrenic subjects showed the largest deficit (Morstyn et al., 1983). This report has been confirmed by us in three subsequent studies (reviewed below), including a study using off-medication patients, and the schizophrenic-normal control group sensitivity and selectivity has been in the 80–90% range. In topographic analyses schizophrenics showed left < right temporal scalp region voltages while normal controls showed a symmetric or opposite trend.

Anatomical substrates of the P300

Although the P300 likely has multiple brain generators, several lines of evidence are consistent with important temporal lobe sources, especially for recordings at lateral, temporal scalp region electrode sites: (1) Knight et al. (1987) have found that stroke lesions in superior temporal gyrus (STG) diminished auditory P300 amplitude but not ERP components at other latencies, e.g., that of P200. It is possible that STG may be a final common pathway for neural activity underlying the P300; (2) depth recordings indicate the presence of P300-like activity with polarity reversals indicative of generator sites in temporal-lobe limbic structures (amygdala and hippocampus), and the same depth recordings have indicated that at least some deep temporal lobe slow waves may be recorded at the surface (see review in Halgren, 1986; and our discussion in McCarley et al., 1989). Important new data on temporal lobe epilepsy (TLE) patients indicate hippocampal/limbic cellular loss whose extent is highly correlated (r = 0.72) with the degree of P300 abnormality in temporal lobe depth recordings (Wood et al., 1989; also McCarthy et al., 1987, 1989). Furthermore, in those TLE patients with preoperative scalp recordings, there was a reduction in P300 amplitude at scalp lateral electrode sites on the affected side. Thus, for left TLE with hippocampal cellular loss, P300 amplitude was reduced 40–50% at T3, with a slightly lesser reduction at F7 and much less at T5. Post-opera-
tively, patients with resection of anterior temporal lobe show similar reductions of P300 amplitude at these lateral scalp recording sites (McCarthy et al., 1987; for new data see, 1989); (3) new magnetoencephalographic (MEG) data indicate deep temporal lobe sources of P300 (Arthur et al., 1989), and new techniques of electrical dipole source modeling are also indicative of deep temporal P300 sources (Scherg, 1989, and personal communication); (4) evidence that the P300 abnormalities we record at lateral scalp electrodes in schizophrenia are related to temporal lobe abnormalities in this disorder comes from our own data showing correlations between the P300 recorded at left temporal scalp sites (T3) and the CT signs of left temporal lobe tissue loss (McCarley et al., 1989). Thus, a growing body of evidence is consistent with lateral electrode recordings of P300 as an index of temporal lobe function/dysfunction.

This link between temporal lobe and P300 is important for schizophrenia studies because a number of studies have pointed to the temporal lobe as a site of pathology in schizophrenia. Limbic structures implicated include hippocampus, amygdala, and parahippocampal gyrus (see review in McCarley et al., 1989; andJeste and Lohr, 1989). These data come from postmortem morphometric studies (Bogerts et al., 1985; Brown et al., 1986) with Brown et al. reporting lateralization and left-sided pathology. Similarly, in vivo structural studies have begun to focus on temporal lobe pathology, with reports of temporal lobe tissue loss in both CT and MRI studies, including those implicating temporal lobe limbic systems and, in a recent preliminary report, the neocortical superior temporal gyrus (Barta et al., 1989), a locus of special interest since STG lesions nearly abolish the P300.

It is also noteworthy that left temporal/limbic system abnormalities have been suggested by previous studies of schizophrenia EF G spectra and EP studies utilizing EEG spectral analysis and EPs (e.g., see early review in Torrey and Peterson, 1974; Dymond et al., 1978; Fenton et al., 1980). Other investigators using similar auditory P300 paradigms have recently confirmed our findings of lateralized P300 reduction in schizophrenia (Ford and Sidman, 1988; Tore110 et al., 1988; personal communication). A study using a different P300 paradigm has not found a lateralized reduction (Pfefferbaum et al., 1989), perhaps because different P300 tasks activate different brain generators, in addition to possible factors of subject variability and differences in data analysis methods. It is to be emphasized that unilateral source generator deficits may produce quite subtle lateralizing effects in scalp recordings; dipole modelling techniques have provided insight into how nearly symmetrical scalp voltage distributions are produced by unilateral lesions of generators in deep temporal lobe (Scherg and Von Cramon, 1985, 1986, 1990). Recent cerebral blood flow studies are also compatible with a left hemisphere abnormality in schizophrenia (Gur et al., 1985). It is of note, however, that PET studies measuring glucose metabolism and xenon cerebral blood flow studies have primarily described abnormalities in the frontal lobe, and unfortunately generally have not been able to detect functional temporal lobe features that might be associated with the temporal lobe pathology described in neuropathological and CT/MRI studies (an exception is DeLisi et al., 1989). These PET techniques may require more temporospatial concentration of metabolic/CBF changes than were present during the long time window demanded by these techniques and than was occasioned by the experimental tasks thus far tested. Thus, the present data suggest P300 studies may have a special role in indexing functional correlates of structural pathology of temporal lobe.

EVALUATING EVENT-RELATED POTENTIAL EVIDENCE FOR P300 COMPONENT ASYMMETRY: METHODOLOGICAL ISSUES

Topographic mapping procedures using color-coding of voltages have become quite widespread since they were introduced by Duffy (see, 1982; also Duffy et al., 1981). Duffy termed his method ‘brain electrical activity mapping’ or BEAM, now a brand name for one commercial system. Other, non-proprietary abbreviations are in common use; we prefer the term brain potential imaging or BPI because of its parallel with other imaging techniques. Topographic mapping has undergone a rapid evolution over the past several years. Our P300 studies have developed in parallel with the
217

field, and it thus is appropriate to place our studies in the context of that methodological history.

Morstyn et al. (1983) were the first to present evidence of left sided P300 deficits in schizophrenia. This study used an exploratory data analysis device known as $t$ statistical probability mapping ($t$-SPM; see Duffy et al., 1981). This procedure calculates $t$ values for group amplitude differences at every scalp electrode site with the goal of identifying time intervals and electrode sites which maximize statistical differences between groups. Limitations of this procedure are that (1) it does not control for inflated ‘type I’ errors due to multiple $t$ tests; (2) it does not take into account the lack of independence between electrode sites; and (3) it cannot distinguish between scalp regions which are statistically significant due to mean amplitude difference or due to differences in variance, a distinction critical for the determination of scalp voltage asymmetries. Since the Morstyn et al. (1983) study was limited to a $t$-SPM analysis, these data suggested the possibility of a P300 asymmetry, but were not statistical confirmation. Although we felt $t$-SPM was important for exploring data, we also felt that because of its statistical inadequacies a follow-up study should meet the following minimal criteria: (1) it should be replicated in independent samples using conservative MA-NOVA (discussed below); (2) it should evince some degree of group specificity, for example, by nonrandomly classifying previously unevaluated individuals into groups; (3) it should show nonrandom correlations with relevant but methodologically independent measures (e.g., clinical symptom measures); (4) it should be consistent with the neurophysiological context, for example, putative source generators (e.g., depth recordings, Scherg’s dipole modelling), or known pathophysiology (e.g., lesions, etc.). (Faux and McCarley (1990), give a detailed step-by-step description of the quantitative methods).

In a follow-up study with the above goals in mind, Faux et al. (1988a) using identical protocols statistically validated the presence of this P300 asymmetry in schizophrenia. One-way multivariate analysis of variance (MANOVA) was used which provided three main classes of information: (1) overall P300 amplitude, which was statistically lower in schizophrenics than normal controls; (2) MANOVA demonstrated group topographic differences based on a test of interaction between groups and electrode sites known as the ‘profile analysis of parallelism’. An example of this (see Fig. 4) is a comparison of the mean integrated amplitude of the ERP over the P300 interval (296–396 ms) for a band of electrodes running from left temporal to right temporal region (i.e., left temporal (T3 and T5), left centroparietal (C3 and P3), midline-centroparietal (Cz and Pz), right centroparietal (C4 and P4), and the right temporal (T4 and T6)); (3) finally, MANOVA provided a test of individual electrode sites based upon Hoteling’s $T$ criterion (a variant of a ‘protected’ $t$ test). These results showed that left temporal electrodes provided the strongest statistically significant separation between groups.

Based upon Morstyn et al.’s (1983) original $t$-SPM scalp feature Faux et al. (1988a) were able to correctly classify seven of nine normal controls and nine of 11 schizophrenics. Shenton et al. (1989b) provided additional evidence of the validity of this feature by showing, as predicted by our hypothesis of a constellation of temporal lobe pathology-P300

![Fig. 4 Comparisons of P300 mean integrated amplitudes (296–396 ms) in normal controls and medicated schizophrenics on a band of electrodes extending from left to right temporal scalp region. Statistical comparisons are made using the protected $t$ scores of Hotelling's $T$ squared analysis. There was a statistically significant difference ($P < 0.05$, asterisks) between normals and medicated schizophrenics at the T3 electrode site. There were also topographic differences. These findings (Faux et al., 1988a) with medicated patients replicated those of Morstyn et al. (1983) in that the T3 electrode maximizes the statistical difference between groups, and that there were left vs right sided P300 differences in schizophrenics.](image-url)
abnormality-positive symptoms, strong correlations between P300 left temporal scalp region amplitude and positive symptoms as measured by Andreasen’s (1984) SAPS scale and the Johnston-Holzman (1979) TDI. This finding has since been replicated (unpublished data).

Our most direct link between P300 abnormalities in schizophrenia and structural abnormalities comes from a recent CT study (McCarley et al., 1989) where we have shown that widening of left sylvian fissure, a putative indicator of temporal lobe tissue loss, in nine schizophrenics was not only statistically greater than that of normal controls, but correlated with P300 amplitude. These patients, having known left-sided P300 deficits, also showed other signs of temporal lobe tissue loss in right sylvian fissure, temporal superficial sulci, supracellular cistern. Widening was also seen in third ventricle, interhemispheric fissure, frontal superficial sulci, and cerebellar vermal sulci. Widening was also seen in third ventricle, interhemispheric fissure, frontal superficial sulci, and cerebellar vermal sulci. Lateral ventricular brain ratio was not statistically significant ($P<0.10$), but the trend indicated slightly larger ventricles in schizophrenics. Again, these data confirmed our overall suspicion that there is a relationship of temporal lobe disease and schizophrenia, and further, gave us a more direct link between structure and electrophysiology. We regard these findings as exploratory and preliminary, but these data now allow us to generate hypotheses in future data sets using higher resolution MRI scans, concurrently being conducted.

Additional replications of P300 asymmetry

Our initial studies, reviewed above, used the linked-ears reference on neuroleptic medicated patients. These variables represented potential confounds in the sense that they could distort electrophysiological differences between schizophrenics and normal controls. We thus review two studies addressing these issues.

(1) Reference site effects. Why was linked-ear reference an issue? A single EEG channel represents the potential difference between two electrode sites, with one electrode site presumably over an active brain site and the other electrode placed at a relatively inactive reference site. The resulting waveform, if the chosen reference site is truly inactive, represents voltage fluctuations primarily from the site of interest. One of the most common reference sites in EEG studies is the so-called linked-ears reference (LER). This reference site is often chosen because linked-ears can cancel out extraneous jaw muscle artifact resulting in a cleaner signal. Unfortunately, given the likelihood that our ERP measures, especially P300, are partially generated from temporal lobe structures, it is also possible that linked ears could cancel out important temporal lobe activity, and worse yet, distort measurements in such a way that activity from each hemisphere is measured unequally.

In our strongest demonstration of P300 asymmetries to date (Faux et al., 1990), we systematically compared P300 topography using the LER with that of a reference site not likely to induce any topographic distortion, the nose reference (NR). We obtained auditory LER and NR P300 data from 20 schizophrenics and 20 normal controls.

Fig. 5 shows grand-averaged waveform data for the linked-ears and nose reference. Note, first of all, that schizophrenics have much lower P300 amplitudes over the 300–400 ms interval over widespread portions of the scalp. Also, note that over this interval right sided electrodes in schizophrenics are slightly larger than corresponding left-sided sites. This is illustrated more dramatically in Fig. 6 where schizophrenic voltages are scaled such that maximum and minimum voltages in this group equal those in normals. The result clearly shows the topographic asymmetry present in schizophrenics. Also of note are the similarity in distribution across electrode sites within groups for both linked ears and nose reference sites, and the fact that a 2 μV cutoff criterion in the linked ears condition correctly classified 90% of the subjects in each group. These results were our third replication of P300 asymmetries in schizophrenia, and further suggest that the linked-ears reference does not greatly influence the detection and measurement of this effect.

(2) Medication effects. Current evidence clearly suggests that neuroleptics are not responsible for the overall P300 amplitude reduction seen in schizophrenics (e.g., Pfefferbaum et al., 1989). In fact, it appears that medicated patients produce P300 voltages which are intermediate to those of unmedicated patients (low end) and normal controls (high end). Topographic distribution, however, may be more sensitive to medication. Pfefferbaum et al. (1989) in an auditory paradigm found P300 maxima at Pz (midline parietal) in unmedicated
Fig. 5. Grand-averaged P300 waveforms (count condition) for schizophrenics and normal controls referred to linked-ears and nose references (Faux et al., 1990). Note that schizophrenic versus normal control group differences over 300–400 msec are generally larger at left-sided electrode sites than at homologous sites on the right. Voltage origins at time zero were determined by a 16 ms prestimulus interval (not shown).

Fig. 6. Normal control versus medicated P300 topographic differences using normalized data (Faux et al., 1990). Group-by-electrode-site interaction effects were tested using a MANOVA profile analysis of parallelism. Normal controls (A) showed a L = R symmetry in contrast to schizophrenics (B) who showed L < R amplitudes.
schizophrenics and normal controls, but P300 maxima at Cz in medicated patients. Thus, it was important for us to determine the effects of medications on our measurements of P300 asymmetry. Here, we review P300 data taken from patients who were neuroleptic-free for at least 14 days (mean = 18 days).

Fig. 7 shows the grand-averaged P300 waveform data from 11 schizophrenics and 11 normal controls (Faux et al., 1989). The trends in these waveforms show left scalp less than right scalp P300 amplitudes for schizophrenics and approximately left equal right amplitudes for normal controls. P300 component peak latency at Cz in schizophrenics had a mean of 429 ms which was significantly longer than the normal control mean of 388 ms. Exploratory t-SPM analysis indicated that the largest statistical schizophrenic versus normal control group differences were at the left middle and posterior temporal region. Topographic differences were confirmed by MANOVA. Our 2 μV cutoff criterion, as shown in Fig. 8, correctly classified 10/11 normal controls and 9/11 schizophrenics.

These data imply that temporal scalp region left less than right P300 asymmetries are present in unmedicated schizophrenics. Interestingly, this was the first study in our laboratory where P300 latency differences were found. This effect has been seen in other studies and could reflect sample differences. In comparison with Pfefferbaum et al. (1989), P300 maxima in unmedicated patients were at Pz, instead of Cz, a finding that is consistent with our previous studies of medicated patients.

Fig. 7. Grand-averaged P300 waveforms of normal controls versus unmedicated schizophrenics (Faux et al., 1989). Schematic depiction of electrode placements of displayed waveforms is also displayed. Note that schizophrenics show left < right P300 amplitudes and that normal controls show approximately left equal right P300 amplitudes.
Left Temporal (T3) Electrode

Fig. 8. Classification based on our previously defined criterion of mean integrated P300 amplitude (300–400 ms) of normal controls and unmedicated schizophrenics at the T3 electrode site and our previously defined criterion level of 2 μV. Note that only one normal control and two schizophrenics were misclassified, a sensitivity of 82% and selectivity of 91%, values comparable to those in previous studies (Faux et al., 1989).

The presence of an asymmetric P300 scalp distribution is consistent with the notion that a pathological process has modified, perhaps unilaterally, the characteristics of source generators in schizophrenia. Although ERPs cannot unambiguously localize underlying source generators, we believe the presence of a P300 asymmetry in schizophrenics implies a pathological process.

ABNORMALITIES OF THE N400 IN SCHIZOPHRENIA

Our interest in the relationship between ERPs and schizophrenic thought disorder, as exemplified in the P300-Thought Disorder Index correlations, has naturally led to an investigation of the N400 in schizophrenia. The pioneering work of Kutas and her colleagues (e.g., Kutas and Hillyard, 1984; for review see, Kutas and Van Petten, 1988) has shown that an ERP negativity with a peak latency near 400 ms (N400) is of maximal amplitude to sentence final words that are semantically anomalous and is small or nonexistent to best completion sentence endings. In fact, Kutas and Hillyard (1984) have demonstrated that the amplitude of the N400 is a monotonic function of the semantic expectancy (cloze probability) of sentence final words. That is, N400 is larger to sentence endings which are semantically the most unexpected and smallest to endings that are highly predictable. In normal subjects, the N400 has proven to be a robust component which is readily evoked by semantic anomalies in the visual and auditory modalities (e.g., Holcomb, 1986). Although we were not aware of any published work on N400 in schizophrenia, we hypothesized that schizophrenics should show a reduced N400, since the N400 may index subjective cloze probability and schizophrenic speech is represented by lower cloze probability sentence completions (Mayer, 1972). In normals, N400 is topographically maximal centrally and at peri-Wernicke's area electrodes with a slight right > left asymmetry for visual stimuli (Kutas and Van Petten, 1988). The left deficit in P300 in schizophrenics led to our prediction that a left deficit would also be found in N400.

Our initial investigation (Adams et al., 1989) has utilized data from eight chronic male, neuroleptic medicated schizophrenics and eight age-matched normal controls without family history of mental illness. All subjects were male, right-handed and had no history of substance dependency or neurological illness. The visual stimuli and protocol were adapted from Neville et al. (1986). Stimuli were constructed from 160 sentence final words which were highly constrained (cloze probability > 0.85) by the preceding sentence context (best completions (BC)). Examples of BC are: 'Every Sunday morning people pray in their local church', and 'Birds usually lay their eggs in a nest'. The stimulus materials were randomly rearranged in a manner such that each final word was anomalous (cloze probability < 0.01) given the prior sentence context (anomalous completions (AC)). Examples of AC are: 'Birds usually lay their eggs in a church', and 'Every Sunday morning people pray in their local nest'. The task consisted of 40 BC and 40 AC sentences (pseudo-random sequence). Across subjects, each final word and sentence stem occurred an equal number of times in each condition. Words were sequentially presented at about one word/s. Subjects were asked to judge whether or not the final word of each sentence made sense (pressing a 'Yes' or 'No' button). In the eight normal control subjects, grand-averaged waveforms to AC showed, in contrast to BC, a marked N400 effect in normals and a lesser effect in the eight schizo-
Fig. 9. Comparison of medicated schizophrenics and normal controls for the N400 component of the ERP (Adams et al., 1989).

As illustrated in the AC-BC subtracted waveforms in Fig. 9, the differences between the groups were largest at left lateral electrode sites. At F7 and FTC1 between-group differences were statistically significant by the Mann-Whitney U non-parametric test ($P<0.05$; non-parametric tests are routinely used by us when the $N$ is small, so as to reduce the distortions of non-normality upon $t$ tests). These statistics must be labeled as tentative and exploratory since multiple comparisons were done, although the data, as graphed in Fig. 9, are clearly consistent with a left-sided N400 reduction in schizophrenia. We regard these initial results as promising, and supportive of our hypotheses as to left hemisphere N400 abnormalities in schizophrenia. We look forward to obtaining data from a larger sample of unmedicated schizophrenics and to determining the correlations with our measures of P300 and with our TDI and SAPS/SANS clinical measures.

A MODEL OF SCHIZOPHRENIC PATHOPHYSIOLOGY BASED ON DYSREGULATION OF EXCITATORY AMINO ACID NEUROTRANSMISSION

This last portion of this article, in contrast to the previous data-oriented approach, sketches a model of schizophrenia pathology that, while speculative in the sense of going beyond current knowledge, is congruent with the known data of both clinical and basic neuroscience research. This initial description is restricted to outlines of key concepts, has limited literature citations, and
leaves details to a future paper. It is probably not necessary to emphasize that the clinical schizophrenia syndrome is most likely heterogeneous with respect to causes; this model does not exclude other pathologies.

This model was prompted by: (1) the increasing evidence implicating the temporal lobe limbic system as a locus of schizophrenic pathology; (2) the explosion of basic neuroscience knowledge about limbic system cellular biology; and (3) difficulties with currently popular models of schizophrenic pathology. For example, one popular model posits a developmental anomaly, such as disordered cell migration, as the source of schizophrenic pathology*. This class of model appears problematical because it does not specify mechanisms: how is this fixed, developmental deficit translated into a disorder with minimal effects before puberty and often shows deteriorating course after onset? Other models of pathology arising in the pre- or perinatal periods appear to have similar problems. The evidence for genetic factors in schizophrenia based on twin and adoption studies appears quite strong, accounting for about 50% of the variance of the occurrence of schizophrenia. However a genetic model has remained a vague postulate, because of the lack of a specific physiological scenario detailing how environmental influences might interact with a genetic abnormality to produce the clinical symptoms and biological pathology.

The first part of our hypothesis concerns the brain site of pathology (see Fig. 10 for an overview of this and other features of the model). There is now growing empirical evidence that a brain locus of dysfunction/pathology of one major form of schizophrenia is in the temporal lobe limbic system. We suggest that this pathology is clinically linked with 'positive symptoms', e.g., thought disorder, bizarre behavior, hallucinations and delusions. Biologically and physiologically this temporal lobe limbic system disturbance is associated with the ERP abnormalities described in the previous sections. The previous sections have also cited data about the presence of structural (anatomical) alterations in temporal lobe limbic system from both CT and MRI studies in the living and also from post-mortem morphometric studies. Structural alterations in schizophrenics have been reported as particularly prominent in hippocampus and related limbic system structures, such as in the hippocampal input zone of entorhinal cortex.

The limbic system of the temporal lobe consists of structures such as the hippocampus that have a more primitive structure than neocortex ('new' cortex) found, for example in frontal lobe and in sensori-motor cortex. The limbic system has been conceptualized as linking the phylogenetically later perceptual and analytic mechanisms of the neocortex with brain regions controlling emotional reactions**.

Clinically and phenomenologically the postulated association of temporal lobe limbic system abnormalities with a picture of positive symptoms is compatible with the evidence for temporal lobe dysfunction in other clinical disorders, such as the syndrome of temporal lobe epilepsy, where patients may also have delusions and hallucina-

---

* Jeste and Lohr’s recent article (1989) furnishes a general index to the developmental pathology literature; their Table 1 is a specific tabulation of recent temporal lobe limbic system neuropathological studies important for the arguments advanced in this paper.

** Isaacson and Pribram’s volumes on the limbic system (1975, 1985) detail the anatomical and cytoarchitectural definition of the limbic system, its interconnections with other parts of the nervous system, as well as offering extensive functional interpretations of its role in behavior and emotion. Isaacson’s (1987) characterization of the entorhinal cortex component of the temporal lobe limbic system is worth quoting, especially in view of our concepts of the P300, "... the entorhinal cortex may be thought of as sending a digest or summary of what is going on in the cortex, and consequently, the environment, to the hippocampal formation" (p. 494). With respect to the close relationship of the limbic system to schizophrenia, the classic article of Torrey and Peterson (1974) on this subject illustrates how long this concept has been in the literature.
temporal lobe limbic system elements. This factor leading to abnormal development may, at the same time, also lead to neurotransmitter dysregulation post-pubertally.

The specific physiological regulatory problem postulated is one related to excitatory amino acid (EAA) neurotransmission in the hippocampus and/or other linked temporal lobe limbic structures†. We suggest this defect leaves the individual susceptible to the destructive, excitotoxic effects of excitatory amino acids (EAA) when stress produces enhanced noradrenergic discharge and corticosteroid output, both of which potentiate hippocampal excitability and vulnerability to excitotoxicity‡. A large number of recent basic neuroscience studies have documented how, under conditions of ischemia/anoxia, EAA neurotransmission may lead to cellular damage and death. These studies have further found that the risk for damage is potentiated by corticosteroids and by physiological mechanisms that lead to cellular depolarization. The basic mechanism of cellular damage and death is due to increased calcium influx both from the depolarization and also from the ionic gates opened by a particular class of EAA neurotransmission, acting on NMDA (N-methyl-D-aspartate) receptors. In addition to the calcium influx, influx of other ions leads to hyperosmolal-

† Rather than obscure the text with repeated citations, we indicate here general references for the excitatory amino acid discussion. An excellent, relatively non-technical overview of both normal and pathological excitatory amino acid neurotransmission is in Cotman et al. (1989). More specific review articles and their topics include: Cotman et al. (1987, brain localization of EAA receptors); MacDermott and Dale (1987, EAA antagonists); and Gustafsson and Wigstrom (1988, long-term potentiation).

‡ For several years norepinephrine has been known to enhance excitability by reducing accommodation to excitatory input by blocking a hyperpolarizing calcium-dependent potassium current that ordinarily occurs when an action potential is produced (Madison and Nicoll, 1984, 1986). In contrast, the studies on corticosteroid influences are much more recent. Evidence that glucocorticoids worsen cell damage from excitotoxicity comes from experiments showing that chemical adrenalectomy protects hippocampal cells following ischaemia (Morse et al., 1989) and that cortisone, given at dosages commensurate with major stress, enhanced excitotoxicity via mechanisms dependent on an NMDA receptor (Armanini et al., 1989).
L-GLUTAMATE OR
GLYCINE NMDA I&+ ' 'jja* '_ _ _' K'
i
Fig. 11. Schematic of the NMDA receptor-ion channel complex in a neuronal cell membrane. The agonist for the receptor site is NMDA or L-glutamate. The attachment of the agonist to the receptor site (rectangle) leads to opening of the ion channel in the neuronal membrane. A key feature of the NMDA receptor ion channel, in contrast to the ion channels for other excitatory amino acids, is that it allows the passage of calcium ions (Ca²⁺, highlighted) from outside to inside the neuron (in addition to allowing the entry of sodium (Na⁺) and exit of potassium (K⁺) ions). As described in the text, Ca²⁺ is important both in excitotoxicity and in long-term alterations of neuronal properties such as long-term potentiation. Both phencyclidine (PCP) and MK-801 are non-competitive blockers of the ion channel. NMDA neurotransmission has a distinctive non-linear property in that the effect of opening the NMDA channel is dependent on the degree of membrane polarization. At membrane polarization voltages typical of the cell at rest, about -70 mV, the magnesium ion (Mg²⁺) blocks the channel nearly completely; however, this blockage is voltage-dependent, becoming progressively less with membrane depolarization. This progressive decrease in Mg²⁺ blockage produces a positive feedback for NMDA neurotransmission: with opening of the ion channel the membrane potential is depolarized by the influx of Na⁺ and Ca²⁺, more depolarization, less Mg²⁺ blockade, more depolarization, and so on. The glycine site is included in the schematic because this glycine receptor modulates the effect of NMDA.

We do not suggest that the mechanisms of schizophrenic injury are so drastic as the conditions of ischaemia and anoxia. We rather postulate a dysregulation at some point in the neurotransmission-receptor activation-cellular response chain that leaves neurons vulnerable to EAA toxicity, most likely involving NMDA neurotransmission—NMDA-mediated synapses are known to be especially abundant in hippocampus and other limbic system structures. This defect could involve an abnormality in the NMDA receptors, in the modulators of the NMDA response (including modulators both at the receptor complex and also other modifiers of cellular excitability such as the monoamines), in the NMDA intracellular second messengers, or possibly through a NMDA ‘third messenger system’, with altered DNA transcription because of NMDA neurotransmission activation of ‘immediate, early’ gene systems. The latter are also known as proto-oncogene systems and NMDA has been reported to activate ZIF/268, c-fos, c-jun (for example, see Worley et al., 1989).

The deficits seen in neuropathological evaluations of schizophrenics are relatively subtle and do suggest a regulatory, use- and stress-dependent defect, consistent with such a mechanism. During extreme stress a greatly enhanced excitation of temporal lobe limbic system structures may lead to death of some of the neurons. Lesser degrees of excitation may lead to pathological and aberrant excitation with inappropriate linkage of sensory stimuli and internal feeling states, such that the emotional significance of sensory stimuli is inappropriately evaluated.

Given the ubiquity of EAA neurotransmission, it is not surprising that a role for EAA neurotransmission has been postulated in disorders other than schizophrenia, and that data supporting such a role have been reported (reviewed in Cotman et al., 1989). Because of the delayed onset of Huntington’s disease, the data supporting abnormalities of NMDA receptors and a role of excitotoxicity in producing cell loss in the striatum in this disorder are particularly interesting. Data suggesting a role for excitotoxicity at NMDA receptors are also present for seizure disorders, especially in regions with high NMDA receptor density, such as amygdala and hippocampus. Taken together, these data also reinforce the important concept that pathologies of EEA neurotransmission may be both region- and mechanism-specific, as we postulate in schizophrenia, in contrast to the existence of an anatomically and mechanistically ‘global’ EAA pathology.

However, it should be acknowledged that, while the evidence for temporal lobe limbic system lesions in schizophrenia is growing, there is no current large body of evidence that provides direct support to our postulate of NMDA system pathology in this disorder. Kornhuber and colleagues (1989) reported an increase in NMDA receptors in
schizophrenics in various brain regions, including limbic system ([3H]MK-801 binding), but studies on never-unmedicated patients have not yet been done. The subtle deficit proposed by us should not be confused with the so-called ‘glutamate theory’ of schizophrenia, which, in direct analogy with the ‘dopamine theory’ postulates alterations in the production of the quantity of the glutamate-related neurotransmitters, usually a reduction. For example, Kornhuber and colleagues (1984) have suggested glutamnergic underfunction in corticostratial and corticoesolimbic systems. Etienne and Baudry (1987) have proposed that a brain alteration in excitatory neurotransmission, perhaps involving the NMDA receptor, might be involved in both brain aging and in schizophrenia, but their theory suggests less brain alteration/aging in schizophrenia and a decreased NMDA neurotransmission.

Obviously a probe of hippocampal function in living schizophrenics would be useful for experimental evidence bearing on these postulates. There are a number of ways in which the P300 event-related potential (ERP) may be related to the physiology and pathology of the hippocampus, and consequently may act as an index of hippocampal function. The P300 indexes processing of novel stimuli in multiple sensory modalities and we suggest it has, as one anatomical substrate, the integration in hippocampus of input from virtually all sensory and polysensory regions of the cortex. The P300 itself, we speculate, has such a large amplitude in hippocampal depth recordings in humans because it reflects a relatively synchronous activation of hippocampal pyramidal neurons; we consequently propose that EAA neurotransmission is a critical substrate of the P300. In fact, the approximately 100–150 ms duration of the P300 may reflect the participation of the NMDA subtype of excitatory amino acid (EEA) neurotransmission, which has a time course of approximately this duration. It is known that the amplitude of the hippocampal response to inputs is importantly gaited by noradrenergic pathways from the locus coeruleus and we suggest this pathway represents one of the important mediators of attention- and state-related effects on the P300, a postulate in agreement with animal data indicating that locus coeruleus lesions dramatically reduce the amplitude of the primate analog of the P300 (Pineda et al., 1989) and the known state-related changes in locus coeruleus activity (Steriade and McCarley, 1990).

The cognitive operations associated with the P300 involve the processing of unusual stimuli after they have so identified and classified as unusual. This post-evaluation ERP may index processes involved in updating of ‘cognitive hypotheses’ about what is to be expected from the environment. Thus, one may identify a usual stimulus event, then modify the set of expectations about what the world is like. We suggest this cognitive updating may be physiologically associated with long-term potentiation, a neurophysiological mechanism that may underlie long-term neuronal changes. Long-term potentiation (LTP) essentially involves the strengthening of a weak input to a neuron when it is paired with a strong one, a basic property of associative learning, and a phenomenon that typically involves NMDA receptors in the hippocampus (the NMDA-mediated influx of calcium is thought to be important). In fact, we suggest that the activity associated with the P300 in hippocampus may function as a ‘strong’ excitation of hippocampal pyramidal neurons and that the weak input that is associatively strengthened is furnished by the specific connectivity associated with the particular sensory input stimulus.

For schizophrenia, this model suggests that temporal lobe limbic system tissue loss is progressive and is worse in untreated schizophrenia, i.e., with uncontrolled stress. It suggests that the end result of such neuronal damage will be reduced temporal lobe neuronal volume, especially in limbic areas, with a reduced P300 amplitude. However, even before severe loss of neuronal function, the degree of P300 decrement may be graded within the group of affected schizophrenics. Relatively lesser damage may be reflected in a P300 amplitude that is less reduced than in schizophrenics with greater damage. This lesser functional disturbance of the...
P300 (and consequently less neuronal damage) should also be associated with an increased incidence of positive symptoms in this group, i.e., increased thought disorder, bizarre behavior, and hallucinations/delusions, precisely the finding of our laboratory in schizophrenics. The 'end stage' of schizophrenia with a deteriorating course may reflect an accumulation of temporal lobe limbic system damage with a consequent reduction in positive symptoms, which were prominent during the stage with neuronal dysfunction but which tend to 'burn out' with cellular death. This basic idea of association of positive symptoms with cellular damage and disruption in the limbic system, preceding an end-stage of cellular death, recalls the suggestion of Nielsen in 1958 that in the limbic system 'it is not complete destruction which gives rise to psychosis but the irritation during the process of destruction'.

There is an apparent lateralization of limbic system pathology in schizophrenia, with most studies reporting greater neuropathological lesions in the dominant hemisphere (left in right-handed subjects). Similarly, the P300 deficit is greatest on the left. In the model presented here, this lateralization would correspond to a functional lateralization of the extent of use and hence of risk of neuronal injury and death.

The relationship of this EAA model of schizophrenic pathology to experimentally induced psychosis by phencyclidine (PCP, 'angel dust') should be noted. Often in the time period following phencyclidine usage there appears a psychosis that very closely mimics an acute schizophrenic episode, and is distinguished from most other toxic psychoses by its duration of a week or two. As described elsewhere in this volume, phencyclidine is known to have important blocking effects on the ion channel associated with the NMDA receptor. It is tempting to speculate that the schizophrenic-like psychosis results from a disturbance of the NMDA system resembling that postulated here, with receptor blockade followed by receptor upregulation and hypersensitivity. Other pharmacological agents inducing psychosis may act through their actions on hippocampal limbic system. Many of these agents are related to norepinephrine and serotonin; they may act via the locus coeruleus and dorsal raphe modulatory projections to the temporal lobe limbic system. As is also well known, most antipsychotic agents block dopamine receptors, a mode of action that suggested the dopamine hypothesis of schizophrenia. We propose that the neuroleptic-induced dopamine blockade has its antipsychotic effect on important outflow targets of the temporal lobe limbic system. Especially important are the nucleus accumbens and cingulate cortex, both of which are important efferent targets of the hippocampus and are also heavily innervated by dopaminergic projections. The role of cholinergic modulatory input to hippocampus is discussed in the paper by Freedman in this volume.

In closing, we acknowledge the speculative nature of our model. We offer it as a way of stimulating thought and research on specific links between limbic system physiology and schizophrenic mechanisms. We believe a strong point of this EAA dysregulation model is that it posits a specific mechanism for the onset of dysfunction to be age- and stress-dependent: the modulation at puberty by sex hormones and with stress by norepinephrine and corticosteroids. It further offers a specific mechanism for the 'deteriorating course' seen in some schizophrenics (see the paper in this volume by the Bronx VA group on 'Kraepelinian schizophrenics'). The specific links postulated between the P300 recorded at lateral temporal scalp electrodes and both normal and abnormal hippocampal physiology/structure are open to further experimental evaluation, and indeed argue for the importance of such studies.

CONCLUSION AND THOUGHTS ABOUT THE FUTURE: THE ROLE OF ERPs IN SCHIZOPHRENIA RESEARCH

The major premise of 'cognitive neuroscience' has been that neither cognition nor brain function can be understood in isolation, and 'research at one level provides constraints, correction, and inspiration for research at the other levels' (Churchland and Sejnowski, 1988). In that context we have reviewed a large body of electrophysiological data on schizophrenic patients performing cognitive tasks which have revealed significant ERP voltage reductions presumably generated by impaired temporal lobe structures. These same potentials may systematically covary with aspects of disordered...
information processing and with structural impairment in patients. We also have reviewed morphometric and structural studies of schizophrenia providing evidence of tissue loss and cellular abnormalities in hippocampus and temporal lobe input zones. To account for these data, we have proposed a model of hippocampal/temporal lobe limbic system neuronal dysfunction in schizophrenia based on dysregulation of the NMDA form of excitatory amino acid neurotransmission. This defect leads to 'excitotoxicity' and neuronal damage and death. The principal mechanisms is an NMDA-associated influx of calcium ions; this toxicity is heightened by the presence of stress-induced increases in noradrenergic neurotransmission and circulating glucocorticoid hormones. One line of evidence implicating neurons using NMDA neurotransmission is the production of a syndrome closely resembling schizophrenia by phencyclidine (PCP), a drug acting on NMDA receptors.

In terms of the field of ERP research, we suggest the advances in neurobiological knowledge have made it imperative to formulate and test neurophysiological as well as cognitive hypotheses, to investigate how scalp ERP abnormalities might reflect underlying brain processes, an exemplified in this volume by the paper by Freedman et al., as well as our own studies. This approach contrasts with the traditional use of ERPs to investigate disordered information processing, and to provide data for cognitive models. It must be appreciated that recent technological developments in dipole source modelling, MEG, and PET and MRI scanning have improved our ability to localize deficits in schizophrenics; future studies in this decade will likely combine two or more of these technologies to study the same patients. This approach of obtaining independent lines of converging evidence is much like the 'construct validity' approach of traditional experimental psychology, and we have elsewhere described the significant advantages of taking this approach in the field of evoked potentials and psychopathology (Nestor et al., 1989).

This approach and the data reviewed here suggest that simple ERP paradigms, such as the 'oddball' detection task, have not outlived their usefulness. While the vast diversity and complexity of paradigms may be useful from a cognitive psychological modeling perspective, psychological complexity is often achieved at the cost of biological obfuscation. The strategy of simplicity and standardization of stimulus paradigms will increase the chance of understanding the ERP source generators and the biological complexity. Another advantage of the strategy of paradigm simplicity is that such studies may prove particularly useful in the study of large populations to define subgroups and to study possible related deficits in biological relatives. Finally, interlaboratory collaborations to allow consensus findings, to document reliability and replicability are also facilitated by simple rather than complex paradigms.

We offer the EAA 'excitotoxicity' model in the hope that a cellular level hypothesis will focus additional research on hippocampus and temporal lobe. In part it is a response to informal comments by colleagues in the ERP field that they had difficulty in even conceptualizing any neurophysiological conditions that might lead to small lesions and damage of specific ERP generators. More importantly it recognizes the revolution in limbic system cellular biology and the necessity of incorporating these basic neurobiological concepts in models that serve as to guide and goad clinical research.

NOTE ADDED IN PROOF

Since this article was written, we have become aware of two reviews of EAA neurotransmission which discuss the possible relationship to schizophrenia. Both of these articles propose a pathological role for EAA, but have somewhat different emphasis from that of this article. Javitt and Zukin (1990) emphasize a possible reduction in glutamatergic transmission in cortex and temporo-hippocampal functions in schizophrenia, but do not consider the overactivity/neurotoxicity suggested in the present chapter or attempt to link the changes with neuropathology. Olney (1989), in his general review of neuropsychiatric disorders, notes the possibility of an 'autoexcitotoxic' state which would eventually lead to hypofunction. 'Subtle brain damage induced by an excitotoxic mechanism in early life would destroy postsynaptic cells that house the Glu receptor system.' He further reviews articles indicating the great sensitivity of the developing brain to NMDA destruction, and of the
poibility of interference with neurotrophic effects. He concludes that '... in view of the complicated makeup of the NMDA receptor-ino-
phore complex, there are a number of possible mechanisms by which hypofunction of this complex might take place ...'. We consider the growing interest in psychiatry in EAA systems to be important, and look forward to tests able to sort out the different pathological mechanisms. With respect to our notion of a progressive cellular loss, DeLisi et al. (1990) have recently presented preliminary data indicating that some schizophrenics do indeed show progressive ventricular enlargement.

REFERENCES


Andreasen, N.C. (1981) Scale for the Assessment of Negative Symptoms (SANS). Department of Psychiatry, University of Iowa College of Medicine, Iowa City, IA.

Andreasen, N.C. (1984) Scale for the Assessment of Positive Symptoms (SAPS). Department of Psychiatry, University of Iowa College of Medicine, Iowa City, IA.


REFERENCES ADDED IN PROOF

