Psychobiological Markers for Schizophrenia: State of the Art and Future Perspectives

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Introduction and Summary:

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Introduction

The purpose of the panel on psychobiological markers for schizophrenia was to update the state of the art since 1977 when the last report was presented to the American College of Neuropsychopharmacology (Zubin, 1979).

During the past 7 years, several developments have taken place which will affect future marker studies. As far as the etiological models which underlie the markers are concerned, the old neuropathological model has been revived in the wake of the new methodologies for brain scanning. The neurophysiological model has been extended to include more neurohumoral and endocrinological factors and immunological system factors indicating the revival of what used to be called the psychosomatic model (Ader, 1981). In genetics, molecular genetics and mapping (HLA) have developed very rapidly. Some of these advances in etiological models are providing new potential markers for schizophrenia.

Perhaps one of the most striking developments during the past septennial was the provision of systematic structured and semistructured interviews for diagnosis, resulting in a high degree of reliability in the classification of the mentally ill. As a consequence, it became possible to provide research diagnostic criteria based on these interviews and a new codification of the Diagnostic and Statistical Manual—DSM-III (American Psychiatric Association, 1980) laid a firmer foundation for specificity in the search for markers. There has also developed a stronger interest in fractionating schizophrenia and also depression into subcategories. In schizophrenia, the use of positive and negative symptoms and their relation to drug effects has provided some tentative new classifications of subgroups which may provide new markers. The positive symptoms seem to characterize patients during their episode, since the symptoms often wax and wane with the episode. The negative symptoms are alleged to be more persistent but there seems to be some doubt whether they are indigenous parts of schizophrenia (Zubin, in press). Despite these efforts at subcategorization of schizophrenia, there has been a revival of the unitary hypothesis of the functional disorders (Bleuler, 1972; Meltzer, 1984) so that we may find the same markers identifying both the schizophrenias as well as the affective disorders. Another new development has arisen from the results of the long-term followup studies of schizophrenia (Bleuler, 1972; Ciompi, 1980; Harding & Strauss, in press; Huber et al., 1980), which seem to cast doubt on the malignant chronic character that has been attributed to schizophrenia, changing it to a more benign disorder. The vulnerability model also points to a change in that direction, substituting a vulnerability to schizophrenia for the be-

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The Ying-Yang Hypothesis of Opioid Peptide Immunomodulation

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Mu and Kappa receptors—downregulators of T-cells (deactivation) versus Delta and Epsilon receptors—upregulators of T-cells (activation)

In 1979 Wybren et al. reported that morphine depressed formation of active T-cell rosettes while methionine enkephalin enhanced formation of active T-cell rosettes. In addition, Brown et al. (1974) reported that responsiveness to mitogen was reduced in heroin addicts. Increases in PHA-induced blastogenesis as well as increases in formation of T-cell rosettes by both methionine and leucine enkephalin were reported by Plotnikoff and Miller (1983).

The above studies led to the hypothesis that there are different opioid receptors on T-cell lymphocytes. At the same time, several outstanding reports appeared indicating that the major peripheral source of the opioid peptides was from the adrenal medulla (Bloom, 1983; Udenfriend & Kilpatrick, 1983). In this regard, Evans (1983) reported that proenkephalin A was common to all species in the adrenal medulla while man had, in addition, the pro-opiomelanocortin hormone. The presence of prohormones led to the findings that different fragments had preferential binding for the various opioid receptors (Herz, 1984). Peptide E and F as well as the heptapeptides bind to mu and kappa receptors while the final end products, enkephalins and endorphins, bind preferentially to delta and epsilon receptors but also, in part, to mu receptors. It is also possible that there are “interactions” between the different receptors (cooperativity).

The final outcome of immunomodulation by these various prohormone fragments may be determined by various stressors resulting in different fractions of individual fragments released into the bloodstream and thereby resulting in either immunosuppression or immunoenhancement. Release of different types of fragments may also account for differences seen between acute versus chronic stress and different stressors, as well as coping behavior (mood states).

References


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the polygenic model can also be dealt with in
lieu that it is a persistent deteriorating process.
This vulnerability may or may not lead to ep-
isodes, but the episodes according to the vul-
nerability model, are intermittent, leading
eventually to a good outcome in the majority
of patients. (Bleuler, 1972; Ciompi, 1980;
Harding & Strauss, in press; Huber et al., 1980).
Thus, episode markers may assume greater
importance because they can help in deter-
mining beginnings and ends of episodes.

One methodological innovation during the
past 7 years was the introduction of informa-
tion processing procedures in the quest for
markers (Kietzman et al., 1984). Since one of
the behavioral deviations in schizophrenia is
in the domain of information reception and
transmission, especially in the cognitive do-
main, it is clear why information processing is
so important in the search for markers. In ear-
lier days, the mere finding of a difference be-
tween schizophrenic and non-schizophrenic
patients and normals, was regarded as a re-
markable achievement in itself. Today, such a
finding is only the beginning. It becomes nec-
necessary to find just where the deviation occurs
in the processing of the information under ex-
amination, in which time period, and how it
relates to the preceding and succeeding pro-
cessing procedures. Furthermore, the vast
knowledge of information processing that has
accumulated in the last few decades in normal
functioning lays the foundation for detecting
deviation in abnormal functioning and thus
provides a solid framework for the search for
markers. Instead of depending upon seren-
dipity alone, a systematic search can be
launched.

The role of information processing in pro-
viding a systematic framework for the search
of markers is most strikingly illustrated in
studies of attention. It is perhaps the most pop-
ular area for schizophrenia research. On the
one hand, in order to be able to carry out any
experimental task, the schizophrenic must ap-
ply attention; but, on the other hand, we hy-
pothesize with Kraepelin and many others that
attention is somehow deviant in schizophre-
nics. How can we trust the outcome of an ex-
periment to reflect performance of the task
itself when deviations in attention rather than
in the functions under investigation may ex-
plain the deviant performance? The results of
many experiments in psychopathology have run
afoul of the general deficit syndrome. The
performance of patients (slowness or less ac-
curacy) may be poor simply because they are
not motivated, do not understand the instruc-
tions, or cannot attend to the task re-
quirements.

Our first attempt to deal with this problem
was to ignore it by designing tasks in which
deviation in attention could probably not af-
fact the results. We chose tasks that resulted
in responses occurring within the first 1,000
msec following stimulation. In such tasks, at-
tention could play either no role or a minor
role because they did not depend upon the
engagement of awareness and cognitions of a
high order, reducing the role of attention to
a minimum. To attain this end, we developed
the cross-modality reaction-time task (Sutton
et al., 1961). This task consists of responding
with the same simple finger lift as each stim-
ulus appears and the reaction time of the cross-
modal stimuli was compared with ipsimodal
stimuli where any deviation in attention, if it
did occur, could cancel out.

Another strategy was to devise tasks in which
schizophrenics excelled normals, so that the
general deficit syndrome could not be used to
explain the results. An example of this type of
strategy is the recent perceptual organization
research devised by Place and Gilmore (1980)
in which schizophrenic patients perform more
rapidly than normal controls under some con-
ditions. This better performance is attribut-
able to the fact that the control subjects’ per-
ception seems to be influenced by the or-
ganizational complexities of the visual stimuli
and they, therefore, take longer to count the
stimuli while the schizophrenics blithely ignore
these organizational complexities and finish the
counting task more quickly.

Another answer to this question was the sta-
tistically controlled design due to the Chap-
mans (1973) which, by the way, was successfully
applied to the cross-modality technique by Ma-
nuzza et al. (1984). They demonstrated that
our initial assumption that attention played no
differential role for normals in the cross-mod-
ality reaction-time task was verified. The dis-
tribution of ipsimodal and crossmodal functions
were found to be psychometrically equivalent
in normals, requiring no equating. It is ironic
that our attempt to ignore attention, though

that schizophrenics display in shifting attention.

In the dichotic listening studies of Dr. Spring, (this issue, p. 509), the various tasks in her experiments were also equated on the normal control group, thus eliminating the possibility of the general deficit syndrome as an explanation of her findings.

Finally, a frontal attack on attention itself was made in such techniques as the Continuous Performance Task (CPT) and Span of Apprehension. Although it is quite clear that these techniques reveal differences between schizophrenics, their unaffected first-degree relatives, and contrasted normal controls, to my knowledge the Chapman argument and the general deficit factor were never addressed in these techniques. Similarly, I do not know whether attention and the general deficit syndrome play a role in the smooth pursuit eye movement task. The fact that Shagass et al. (1976) showed that forcing attention to the numerals on the swinging pendulum reduces the phenomenon, makes one wonder whether attention may not be a factor.* Not all of these measures of attention have been shown to be vulnerability markers and some may turn out to be episode or residual markers.

In the psychosocial sphere, social networks, family deviance and emotional expression in families with highly critical members, as contrasted with nurturing accepting members, have developed prominently as factors in vulnerability, especially in the study of relapses. Whether they can serve as vulnerability markers or episode markers remains to be seen.

The question of whether markers may now serve as the independent variable for classifying mental disorders has arisen. A more equitable approach is the iterative method where either the marker or the diagnostic category can serve alternatingly as the initial entry point. Then the independent variable can change places with the dependent variable, the latter becoming the independent variable and a new analysis made of the data. In this way, both the marker and the diagnostic categories can be further refined.

In line with the need for a "trigger" to trip an episode in the vulnerable, the rapid developments in the field of immunological studies have indicated that stressors seem to lead to a breakdown in the immune system and hence this system could be used to detect triggering stressful events and thus serve to mark the beginnings and ends of episodes (Adler, 1981).

As far as episode markers are concerned, the work on chemical as well as behavioral challenges may show the way for determining the beginnings and ends of episodes (van Kammen, this issue).

As for residual markers, only a comparison of patients who do not show residual markers with those that do, can throw light on the indigenous character of residual markers or defects.

**Future Perspectives**

As for the future, there seems to be a greater tendency to accept the concept of non-familial schizophrenia or phenocopies to use the genetic term. Some of the positive evidence for non-genetic etiology of schizophrenia are the role of perinatal factors, ophthalmological, and other congenital deviations (Zubin, 1979) and the potential of persistent long-term stress for inducing a schizophrenic episode. (Dohrenwend & Dohrenwend, 1981). On the negative side, it seems that the role of penetrance in studies of sporadic schizophrenics has not been fully appreciated. For the monogenic hypothesis, the degree of penetrance is on the order of .25. If this is accepted, it can readily be shown that a minimum of 20 first-degree relatives for a single proband is necessary before dismissing the role of genetics on the .95 level of confidence. Since very few probands would have as many as 20 first-degree relatives, it becomes necessary to examine for each proband separately by means of a four-fold table comparing the number of affected and unaffected first-degree relatives with chance expectancy and the value of chi square computed for each of these four-fold tables. The distribution of these chi square values should not differ from its expected chance distribution if we are to conclude that probands suffer from a nonfamilial disorder. How to determine the minimum number of first-degree relatives for multiple families and for polygenic hypotheses needs to be worked out. If a threshold value for determining the dichotomy into vulnerable-invulnerable individuals can be developed,

*Phillip Holzman has addressed this question in his Dean Award Lecture, in press*
successful in normals, revealed the deviation a manner analogous to the monogenic model and the minimal number of first-degree relatives determined in like manner.

In considering the variety of possible markers (Zubin, in press) it can be shown that in addition to vulnerability markers there are at least two types of invulnerability markers. Thus, a marker which is present premorbidly, morbidly, and postmorbidly but occurs in unaffected first-degree relatives with no greater frequency than chance expectancy, can be regarded as an invulnerability marker since its absence seems to protect the first-degree relatives from developing an episode. By the same token, if a marker occurs in the unaffected first-degree relatives with a frequency exceeding chance, but does not occur in the probands, it could be interpreted as an invulnerability marker, since its presence in the first-degree relatives probably protects them against developing an episode, and its absence in the proband permitted the development of an episode.

At this point one may raise the question of what is meant by a genetic disorder. Since, in the last analysis, the human organism can react only in ways permitted by its genome, every disorder must be genetically compatible with the genome of the organism. What then is meant by a genetic disorder? Woodworth (1941) long ago pointed out that the relative proportion of the variance of a trait attributable to hereditary or environmental factors is what determines our decision as to whether the trait is hereditary or environmental in origin. Thus, if all the members of the group under study have identical genomes, any variation in a trait must be due to environment and mutatis mutandis for identical environments. But even such disorders as phenylketonuria (PKU) or Tay-Sachs disease may be genetic disorders only in our social-cultural physical environment. Perhaps we call a disorder genetic when we have some evidence for genetic transmission but are ignorant of the required environmental assists. Similarly, we may call a disorder environmental when we know the noxious environmental agents but have not yet discovered the genetic factors.

Finally, the increase in interest in psychosocial aspects of vulnerability, though it may not contribute to etiology (although some the-

orists claim that it does) (Dohrenwend & Dohrenwend, 1981) certainly contributes to the triggering, maintenance, and recurrence of episodes. It becomes necessary to determine the link between external factors producing stress with the internal responses to stress in the immunological, endocrinological systems in their interaction with the central nervous system. The study of the psychosocial factors may lead to a better understanding of chronicity and recidivism, and may point to the entry path for intervention.

It is also important to determine whether the markers are associated with the disorder (pathophysiological markers) or have no direct association with the disorder (linkage type). The former may be prodromal in character in so far as they may develop only after the incipient onset of the disorder and hence may serve as episode markers than vulnerability markers, although some markers may serve both as episode and vulnerability markers, e.g., P300. The linkage type markers may occur coincidentally with schizophrenia rather than causally, e.g., are located on the same chromosomes close to the alleles determining schizophrenia, and hence can be depended upon to distinguish unaffected first-degree relatives. Pathophysiological markers that occur in unaffected first-degree relatives, strengthen the possibility that they are at least in part vulnerability rather than episode markers.

It should also be borne in mind that not all individuals will develop an episode even if they possess the marker identifying them as vulnerable and are subjected to sufficiently noxious stressors. Certain moderating variables such as social networks, ecological niches, and premorbid personality may absorb the stress and prevent the episode if they are favorable, or enhance the probability of a developing episode if they are unfavorable (Zubin et al., in press).

Finally, the response to treatment may itself serve as a marker, differentiating those who benefit from those who do not.

Summary of Panel Presentations

Some of the outstanding contributions of the present panel summarizing the state of the art as of 1985 are as follows:

Generally, markers of vulnerability can be
found not only in the genetic domain but also in any of the other seven domains of the etiological models of schizophrenia (Zubin, 1981). One model, the neurophysiological model, seems to possess certain transcending characteristics which need to be pointed out. Since neurophysiology underlies all behavior, deviations in this carrier wave for behavior should accompany any of the disordered behavior by which we now recognize the presence of schizophrenia. As an example, P300 transmits the characteristics of the stimulus which elicits it, appearing independently of the modality in which it arises and of some of the other properties of the stimulus which elicits it. Hence, it becomes an independent indicator of brain function, independent of its origin, and is an endogenous brain response to stimulation. Consequently, P300 and other components of the event-related potentials are excellent measures of the deviations in information processing which characterize schizophrenia. In contrast with other techniques which can not always transcend the concrete matrix from which they emanate, physiological indicators may be free of them. It may serve the same purpose in analyzing brain function that factor analysis serves in analyzing the common elements in many performances. Another virtue of physiological indicators is that they can be repeated as often as required (within limits of adaptation). Consequently, the final averaged result is relatively free of noise.

One finding reported by Steinhauer (this issue, p. 513) is that the pattern of response of P300 to the various degrees of uncertainty of the stimulus is quite different in schizophrenics than in normals. This additional possibility of determining a pattern over several degrees of uncertainty makes the analysis more flexible, so that individuals can be clustered in accordance with the pattern they exhibit. Since the likelihood of finding pathognomonic markers is rather low, the pattern across different markers may also help to group individuals into like-minded clusters. Thus, instead of being merely a group phenomenon, the marker or markers can pin-point the single individual and his peers and, therefore, can be used meaningfully in dealing with them.

An interesting example of how the different characteristics of a disorder vary in the degree of their pathognomonicity is found in PKU. Taking the marker of the concentration of phenylalanine in the blood plasma, the distribution for normals is from 0 to about 2%, while the distribution for PKU patients is from about 15% to 40%, with no overlap. However, if IQ is taken as a marker, the distribution for PKU overlaps with the distribution for normals between IQs of 20 and 125. Similarly, in the distribution for head size PKU overlaps with that of normals between 300 and 350 mm. For hair color reflectance, the PKU distribution overlaps with the normal distribution almost completely—from 0 to 30%. However, it is possible that if the pattern of IQ status, head size, and hair color reflectance were obtained for PKU for each patient and for each normal, the overlap between the patterns would be reduced considerably. Our markers for schizophrenia resemble more the hair color reflectance measure than the phenylalanine concentration in blood plasma, and that is why we need to be satisfied with patterns of markers rather than search for pathognomonic markers (Levitan & Montague, 1977).

At present, the beginnings and terminations of episodes are based purely on clinical observations and hunches. Dr. van Kammen has pointed out that it may be possible to develop objective episode markers which would enable us to recognize the imminence of an incipient episode or the imminence of its termination. The ability to perceive the approaching episode may help in the selection of suitable intervention strategies, while knowledge that the episode is terminating may be of value in altering the treatment regimen. The question raised by van Kammen is whether we can find suitable biochemical challenges to serve as episode markers. If this can be done, they could serve as indicators for the beginning and end of treatment. We may possibly be able to abort incipient episodes or prevent needless continuation of drug treatment with its dangers of inducing tardive dyskinesia. Among the candidates for episode markers are 1) growth hormone responses to apomorphine, 2) psychotogenic response to amphetamine and methylphenidate, and 3) relative cerebrospinal fluid/norepinephrine levels (van Kammen, this issue, p. 497).

These challenges can serve as chemical stressors, even as high emotional expression in families serves as an environmental stressors.
The controlled graduated stress which can be induced by amphetamine may serve to trigger a miniepisode in those who are still in their episode while this chemical challenge may produce little or no effect in those in whom the episode is ended. It is likely that behaviorally induced stressors may serve the same purpose (Zubin & Steinhauer, 1981).

In the cognitive domain, Dr. Spring (this issue, p. 509) has added a new marker of vulnerability—intrusions in dichotic listening with distractors, especially in delusional schizophrenics. The performance of these schizophrenics on the shadowing task itself is not impaired but, unlike their controls, they make intrusions from the non-target ear in their shadowing. This holds true not only of the schizophrenic probands but also of their first-degree relatives, and does not seem to disappear in remitted cases. It also does not characterize nonparanoid schizophrenics and nonschizophrenic mental patients and their relatives. Dr. Spring suggests that the deviation in information processing which this marker presents may be due to a difference in the allocation of attention capacity. The schizophrenic may be allocating more processing capacity to performance on this task than normals, without interfering with accuracy of shadowing on the main channel. According to this suggestion, schizophrenics may be excelling in their performance since, despite instructions to monitor only the main channel, they succeed in monitoring even the forbidden channel to some extent.

In the perceptual domain, Dr. Kietzman (this issue, p. 518) has pointed out that the speed of visual information processing is characteristically slowed down in schizophrenics. Two techniques for measuring the speed of processing are now available: span of apprehension and backward masking. Dr. Knight has suggested that the slowed processing may be a long-term characteristic product of a perceptual organization deficiency in schizophrenics with poor premorbid personalities (Knight, 1984).

All in all, the last 7 years have been a period of consolidation and gradual rather than rapid further development. In a sense it was the sabbatical year for markers; nevertheless, the impact of information processing as a framework has been strongly felt. Several of the markers have entrenched themselves more firmly by providing evidence of their existence in unaffected first-degree relatives—a requirement for establishing them as vulnerability markers.

In the 1977 report (Zubin, 1979) the following potential vulnerability markers (as determined by presence in unaffected first degree relatives) were reported: 1) Cancro's measures of eye movements (blinking) during visual mental tasks, 2) Holzman's smooth pursuit eye movements, 3) Cromwell's cross-over index in reaction time, and 4) Rosvold's and Orzack's vigilance task of continuous performance.

Today, the list of potential vulnerability markers is as follows: crossover reaction time, span of apprehension, CPT, backward masking, smooth pursuit eye movements, and dichotic listening with distraction. Those awaiting vulnerability status are cross-modality reaction time, evoked potentials, pupillographic responses, and heart rate.

Very little progress has been made in the area of residual markers, an area which is in need of further development, though it has been suggested that some negative symptoms may qualify as residual markers. The other types of markers and their usefulness are waiting for further research.

References


