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REVIEW/MINI-REVIEW ▸

Information Processing and Attentional Dysfunctions as Vulnerability Indicators in Schizophrenia Spectrum Disorders

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Summary

The schizotypal personality disorder is believed to be part of the schizophrenic spectrum of disorders including schizophrenic patients as well as some of their seemingly unaffected relatives with discreet symptoms. Spectrum-individuals are characterised by a genetic vulnerability for schizophrenia. The vulnerability is connected with neurocognitive deficits independent of clinical state. Some cognitive dysfunctions are unspecific and probably related to non-genetic brain damage. A consistent finding has, however, been poor performance in tasks involving information processing and attention. The findings point to the existence of specific sensory-perceptual deficits or a general attentional dysfunction. Identification of cognitive disturbances characteristic not only of schizophrenics, but also of schizotypal disordered and their relatives in the boundaries of schizophrenia, is relevant in order better to understand the pathogenetic mechanisms and treatment of schizophrenia. In the present review clinical data are analysed based on models of vulnerability and information processing with reference to a characterisation of the neuro-integrative deficits that form the core abnormalities of the spectrum.

Key words: *schizotypal personality disorder, schizophrenic spectrum, vulnerability, information processing, attention.*

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Introduction

The theory of a schizophrenic spectrum originates from the observation that schizophrenics and schizotypal disordered subjects share common clinical traits, and from genetic studies which have documented an etiologic relationship (Parnas 1997). The spectrum encompasses a continuum of conditions ranging from severe, unremitting psychotic schizophrenia to milder, episodic psychotic schizophrenia-like disorders and discreet defects in reality testing and cognitive function in seemingly unaffected relatives to schizophrenic patients or patients with schizotypal personality disorder (Braff 1993).

The schizotypal personality disorder is characterised by a schizophrenia-like symptomatology without psychotic depth. Patients show odd thinking and speech, inappropriate or constricted affect, autistic features, unusual perceptual experiences and pseudo-obsessions. Particularly in response to stress they might experience micro-psychotic episodes with intense illusions, hallucinations and delusions (DSM-IV; ICD-10). The disorder is chronic although 60% never get in contact with the psychiatric system. Only a small proportion of the patients eventually develops schizophrenia (Parnas 1997; ICD-10).

Cognitive[1] impairments have been considered to be core features of schizophrenia since Kraepelin and Bleuler (Braff 1990, 1992, 1993; Dawson et al 1995; Goldberg and Gold 1995). Numerous cognitive tasks have confirmed the existence of specific problems involving aspects of memory, imagining, judging, concentration, generating and executing plans, attention[2], and information processing[3] (Braff 1981, 1993; Dawson et al 1995; Goldberg and Gold 1995; Nuechterlein and Dawson 1984).

Over the last decades there has been a growing interest in elucidating cognitive markers, which hypothetically constitute a common character

1. The term cognition refers to intellectual activities including perceiving, remembering, imagining, conceiving, understanding, reasoning and judging (5).
2. Attention refers to the ability to consciously focus on a particular internal or external experience (1).
3. Information processing refers to the entire range of mental processes that an external sensory stimulus passes through as it enters the central nervous system. It involves identification and classification of information and its source, assessment of its significance, and comparison of it with other incoming information or that stored in memory. The information may or may not be retained, enter consciousness and/or produce a behavioural response (5).

for individuals in the schizophrenic spectrum. Such an identification of a genetic liability or vulnerability indicator for schizophrenia is relevant in order to define a non-clinical schizophrenic phenotype, optimise therapeutic strategy, and ultimately achieve a better understanding of the etiologic and pathogenetic mechanism of schizophrenia (Green and Nuechterlein 1999; Andreasen 1997; Glenthøj et al 1998; Glenthøj and Hemmingsen 1999).

Using schizotypal disordered patients as a basis for the identification of cognitive markers for schizophrenia, instead of schizophrenics, is an experimental advantage because the schizotypals are mostly apsychotic, non-medicated and non-hospitalised. This minimises the risk that a given cognitive task performance is determined by psychosis per se, medication or institutionalisation instead of a genetic liability for schizophrenia (Braff 1993).

Several authors have reported attentional and information processing impairments in schizotypals and other individuals at the border of schizophrenia (Braff 1993; Lenzenweger et al 1991; Nuechterlein and Dawson 1984; Nuechterlein et al 1994). Accordingly, these dysfunctions are believed to be vulnerability indicators for schizophrenia (Lenzenweger et al 1991). Thus, clarifying attentional and information processing dysfunctions is important for understanding the pathogenesis and treatment of schizophrenia and the schizophrenia-like disorders.
In the present review clinical data are analysed based on models of vulnerability and information processing, and relevant cognitive tasks and task-results are summarised, with reference to a characterisation of the neuro-integrative deficits that form the core abnormalities of the spectrum.

Theories of vulnerability
A genetic predisposition is a necessary, but not sufficient, condition for the development of schizophrenia. The predisposition is supposed to be composed of one or more defective genes that cause a vulnerability for development of schizophrenia because they induce a dysfunction in the neuro-integrative system in the central nervous system with a resultant compromised information processing (Braff 1993; Glenthøj 1995; Glenthøj et al 1993, 1998; Glenthøj and Hemmingsen 1997, 1999; Nuechterlein and Dawson 1984).
Environmental influence, including early organic damage of the brain regions involved in information processing, can result in cognitive disturbances which cannot be distinguished from the disturbances brought about by the genetic predisposition. The cognitive disturbances resulting from organic brain damage are, however, often accompanied by more unspecific deficits. Both conditions predispose, according to the hypothesis, to development of secondary disturbances in the transmitters of the brain and psychosis (Glenthøj 1995; Glenthøj et al 1993, 1998; Glenthøj and Hemmingsen 1997, 1999). They are believed - together or separately - to comprise the vulnerability for development of schizophrenic symptoms. Thus, the "core" of the schizophrenias is composed of genetically determined vulnerability indicators rather than observable clinical symptoms (Green and Nuechterlein 1999). The environmentally caused impairments are more heterogeneous and thus less suitable for characterisation of the spectrum. It is, however, necessary to take these symptoms into consideration as they are partly identical with disturbances caused by genetic disposition. Accordingly, they can influence the results of the clinical tasks of cognitive dysfunctions. This has been exemplified by Goldberg and colleagues, who studied monozygotic twins (Goldberg and Gold 1995). Whether an individual who possesses genetically determined defects in information processing and attentional functions develops schizophrenia, depends on both the extent and the character of the environmental factors, and on other genetic factors.
A vulnerability indicator/dysfunction should meet the following criteria:
1. It should be specific for schizophrenic patients compared to a normal population
2. It should be present in both psychotic and asymptomatic periods, and
3. It should be disproportionately present in seemingly unaffected first-degree relatives of schizophrenic patients (Green and Nuechterlein 1999).

Vulnerability indicators can be identified by means of three different experimental designs:
1. By testing schizophrenic patients for stable, symptom-independent dysfunctions
2. By testing first degree relatives of schizophrenics for a disproportional presence of dysfunctions
3. By testing schizotypal disordered patients (Green and Nuechterlein 1999).

Stable vulnerability indicators refer to deficits, which presumably are associated with the genetic predisposition and therefore are present constantly, independent of the clinical state of the schizophrenic patient. *Episodic or symptomatic indicators,* on the other hand, refer to deficits, which normalise in remitting periods. They reflect the presence of apparent clinical disease and not the genetic predisposition. The causality is ambiguous; the deficits may follow the symptoms or be the cause of the symptoms (Green and Nuechterlein 1999). It appears that the stable vulnerability indicators refer to information processing variables independent of the clinical state of the patient, while the episodic or

symptomatic indicators refer to variables dependent on the clinical state of the patient. The schizotypal state can be defined as a subclinical form of schizophrenia with essentially intact reality testing. It is therefore reasonable to believe that it is possible in schizotypal disordered exclusively to demonstrate the presence of stable vulnerability indicators, and not episodic or symptomatic indicators. It is, however, possible that the stable vulnerability indicators are less pronounced in schizotypal disordered than in schizophrenics. That is, the information processing ability of schizotypals is possibly less than that of normal individuals and greater than that of schizophrenics. This might demand a greater sensitivity or difficulty of tasks used to identify information processing deficits in schizotypals relative to schizophrenics.
State and trait variables or markers are apparently synonymous with the terms episodic and stable vulnerability indicators respectively. State-markers refer to information processing deficits characteristic for psychosis per se whether this is caused by schizophrenia, mania, schizo-affective disorder or psychoactive drugs. Thus, state-markers are diagnostically unspecific and point out the possibility that information processing dysfunction might be a common feature of psychoses. Trait-markers refer to genetically associated deficits present in both schizophrenic patients in remission/antipsychotic treatment and in "boundary-individuals" such as schizotypals, high-risk children of schizophrenic parents and seemingly unaffected relatives of schizophrenics (Braff 1993).

Models of information processing and attention

Since the 1960s and 1970s, models of information processing have played a dominant theoretical role in the experimental research into cognitive dysfunction in psychiatric patients (Rund and Landrø 1990; Siegel 1995). Siegel (1995) has depicted a basic model of information processing as illustrated in a modified version in fig. 1.

The attentional function controls the flow of information processing. Theoretically, it can be divided into three different qualities; vigilance, capacity and selectivity respectively (Siegel 1995). Vigilance refers to continuous or sustained attention (Nuechterlein and Dawson 1984; Siegel 1995), or the intensity of the attention (Parnas 1997). *Attention capacity involves* the idea that attention theoretically is characterised by a pool of attentional resources that limit the amount of stimuli processed at a given moment. A task with a high information processing load draws relatively more resources than a task with a low processing load, and therefore lessens the resources available for other simultaneous tasks (Nuechterlein and Dawson 1984; Siegel 1995). Cognitive models, which speculate on the existence of several resource pools, propose a central executive unit involved in the resource allocation (Lenzenweger et al 1991; Siegel 1995). Concordant with this idea, other theories argue that an individual is able to process only a limited amount of the total incoming information, which is selected by means of a "filter" or a "bottleneck" structurally involving the cortico-striato-thalamo-cortical circuits (see Glenthøj et al 1998 and Glenthøj and Hemmingsen 1999), but localised to an obscure stage in the information processing cascade (Carlsson 1988; Rund and Landrø 1990; Siegel 1995).

Selective attention is the ability to process a sensory input selectively. Hypothetically, it involves two different processes; *preattentive processing* and *focal attention or attentive processing* respectively (Nuechterlein and Dawson 1984; Rund and Landrø 1990; Siegel 1995). Preattentive processing detects stimuli in the sensory memory and performs a quick, preliminary, global and holistic analysis of the information. The process is automatic and demands little or no conscious attention - that is, it is not capacity-restricted - and is difficult to depress voluntarily (Dawson et al 1995; Nuechterlein and Dawson 1984; Rund and Landrø 1990; Siegel 1995). If the stimulus is new or important, preattentive processing is followed by attentive processing, which performs a slower and more detailed analysis of the information. Unlike the former, this process is controlled and demands allocation of attentional resources - that is, it is capacity-restricted, interferes with simultaneous controlled processes, and can be depressed voluntarily (Nuechterlein and Dawson 1984; Rund and Landrø 1990; Siegel 1995).

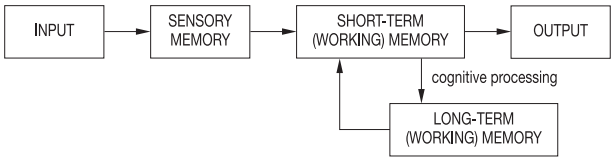

Figure 1
Information Processing Model: In the initial stage, sensation, an external stimuli is transformed into a mental representation, which is encoded into a sensory memory for a short while (250 msec). Here the information is processed into perceptual data. Using the short-term (working) memory the data are analysed, encoded into long-term memory, and retrieved from long term-memory to short-term (working) memory. Representations in long-term memory are available for cognitive processing - e.g. generalisation, deduction, comparison - as they are retrieved back into working memory. Thus, the retrieval process might modify the original data stored in long-term memory. Modified from Siegel (1995).

Information processing and attentional dysfunctions in schizophrenia spectrum disorders:

Stable vulnerability indicators or trait-markers for schizophrenia?

Information processing and attentional dysfunctions in spectrum-individuals can be identified by means of various cognitive tasks. Below, techniques which have revealed deficits in both "boundary-individuals", including schizotypals, and in schizophrenics - that is, possible stable vulnerability indicators or trait-markers - are brought into focus. Moreover, the observed deficits are interpreted according to theoretical models of information processing.

Visual Backward Masking

Visual Backward Masking is a cognitive task of the earliest stages of the visual information processing. The trial individual is initially presented for an informative target stimulus - e.g. the letter T - for a time span only just allowing him or her to detect the stimulus. Following a short interstimulus interval (ISI), the individual is presented for a new, non-informative masking stimulus - e.g. lines of Xs. The term masking relates to the observation that all trial individuals will report having seen the masking stimulus, but not the target stimulus, at short ISIs. The term backward means that the masking stimulus follows the target stimulus. Schizophrenic spectrum subjects perform less well than controls at certain ISIs: i.e. patients do not see the target stimulus at ISIs where the normal controls do.

Several studies have reported deficits in schizophrenic patients in the first 500 msec following stimulus input (Braff 1993; Braff and Saccuzzo 1985; Rund and Landrø 1990; Rund et al 1996; Saccuzzo and Braff 1986; Siegel 1995). Analogous deficits have been demonstrated in "boundary individuals" (Braff 1981, 1993; Nuechterlein and Dawson 1984; Green and Nuechterlein 1999; Rund and Landrø 1990). Braff (1981), for instance, found no significant difference in mean target stimulus detection rate between non-medicated schizotypals and medicated schizophrenics at 300 msec ISI. Furthermore, both schizotypals and schizophrenics performed less well than controls of non-medicated, non-psychotic depressive patients at an ISI of 300 msec. These findings demonstrate that the deficit in backward masking is not an artefact to anti-psychotic treatment, and that the two groups of "spectrum-patients" have an information processing dysfunction in common, which hypothetically could make up part of the vulnerability for development of psychotic schizophrenic symptoms. It would have been preferable had Braff (1981) included a normal control group in the trial. Only in this way would it have been possible to demonstrate whether the dysfunction is specific for patients in the schizophrenic spectrum; that is, related to a common genetic substrate. It is possible that depressive patients manifest poorer task-result compared to normal controls. If this is the case, the observed dysfunction might reflect psychopathology per se rather than a vulnerability indicator for schizophrenia. Rund and colleagues (1996) actually found identical, significant masking-deficits in young ADHD (Attention Deficit Hyperactivity Disorder) patients and young "spectrum-patients" at 49.5 msec ISI. Saccuzzo & Braff (1986) did not observe significant differences in masking deficits between schizophrenic, schizoaffective and bipolar affective patients, but did reveal significantly poorer task-performance in these patients compared to non-psychotic depressed patients. Accordingly, they had to conclude that impaired information processing could be a state-marker that co-varies with the presence of disturbances of thinking and psychotic symptoms. Founded on empirical evidence on deficits in non-psychotic schizophrenics and schizotypals, Saccuzzo & Braff stated, however, that the dysfunction also could be a constantly present trait-marker for patients in the schizophrenic spectrum. The diagnostic specificity for the spectrum of schizophrenia has been supported by Green & Nuechterlein (1999) among others. They observed masking deficits in both siblings of schizophrenics and in non-medicated remitted patients compared to normal controls.

The exact mechanisms determining the masking phenomenon and the masking deficits mentioned are obscure. Several interpretations are possible:
If the masking effect is determined by sensory-perceptual mechanisms, two different causes of the deficits in "spectrum patients" are possible - disturbances of interruption and integration respectively. Thus transformation of information from the labile sensory memory to the short-term memory might proceed at a relatively slower rate in "spectrum patients" than in others (fig. 1). The result would be that presentation of the masking stimulus would interrupt processing of the target stimulus. It is also possible that impaired perceptual sensitivity in "spectrum-patients" combined with integration of the masking stimulus in the target stimulus is responsible for the pronounced masking effect (Green and Nuechterlein 1999; Nuechterlein and Dawson 1984; Nuechterlein et al 1994; Saccuzzo and Braff 1986).

If the masking effect involves attentional functions, the deficits in "spectrum individuals" might reflect an increased vulnerability for attentional disengagement from one object to

another, i.e. from target stimulus to masking stimulus (Green and Nuechterlein 1999; Nuechterlein et al 1994).
Another possibility is that the observed masking deficits are the result of a more general dysfunction rather than a specific sensory-perceptual deficit (Saccuzzo and Braff 1986). Thus, a trait-marker in "spectrum patients" might consist of alternating under and over provision of information, both phenomena causing cognitive deficits. Informational underprovision might be determined by a generally reduced rate of information processing, while overprovision could be caused by inappropriate allocation of resources to the processing of masking stimulus - this would be consistent with theories on defect filter functioning in schizophrenia (Carlsson 1988; Glenthøj et al 1993; Nuechterlein et al 1994). Saccuzzo & Braff (1986) also call attention to the fact that the psychotic stage per se reduces the processing resources of the patient; this might explain why masking deficits can be state-markers too.

Continuous Performance Test
Continuous Performance Test (CPT) is a visual vigilance task, which tests the ability to sustained attention for a fixed period of time. The test individual is presented with a random sequence of repetitive visual stimuli - single letters or numbers - each presented for 40-200 msec with ISIs of 1-2 sec. The test individual is instructed to press a response button each time an explicit target stimulus appears. The momentary load of the information processing system can be varied from presentation of a simple, distinct target stimulus (low processing load) to presentation of perceptually degraded target stimuli or target stimuli composed of sequences of two consecutive letters or numbers (high processing load).

Two mutually independent performance indices, *sensitivity* and *response criterion*, respectively, are employed to asses the test performance. Sensitivity relates to the ability of the test individual to discriminate target stimuli from non-target stimuli, that is, signal-noise-discrimination. High sensitivity generally correlates with a high target stimulus response rate and a low non-target stimulus response rate. Response criterion refers to the amount of perceptual evidence necessary for the test individual to decide whenever the stimulus is a target stimulus or not.

Empirical data describe CPT deficits in patients in the schizophrenic spectrum (Braff 1993; Epstein et al 1996; Lenzenweger et al 1991; Nuechterlein and Dawson 1984; Nuechterlein et al 1994; Rund and Landrø 1990; Siegel 1995). Deficits are demonstrated in both "boundary individuals" and acute psychotic and remitted schizophrenic patients (Nuechterlein and Dawson 1984). Diagnostic specificity for the schizophrenic spectrum is supported, among other things, by the observation that schizophrenic patients manifest more pronounced deficits than do affective disordered, non-psychotics and alcoholics (Nuechterlein and Dawson 1984; Rund and Landrø 1990), and by the fact that CPT deficits are associated with a genetic predisposition for schizophrenia (Nuechterlein and Dawson 1984).

Epstein and colleagues (1996) have tried to disprove the possibility that the performance of schizophrenic patients is an artefact related to anti-psychotic treatment. They found a non-significant effect of anti-psychotic treatment on CPT performance. The validity of this result is, however, doubtful, as a great proportion of the patients included in the study were either completely or partially resistant to the therapy. Using the complex version of CANTAB Rapid Visual Information Processing task, which is akin to the classic CPT with high processing load, Fagerlund and colleagues (1999, Unpublished data), however, observed an effect of medication on sensitivity in drug-naive, first-episode schizophrenic patients. The finding supports a state-related sensitivity to perceptual load that can be considered, at least in part, accessible to treatment. It is also in agreement with Nuechterlein and colleagues (1994) who found that the CPT consists of a stable vulnerability indicator and a state-related indicator varying with perceptual load, vulnerability and state.
Deficits in schizophrenic patients can be observed by means of tasks with a low information processing load, while analogues deficits in "boundary individuals" can be revealed by application of tests with a high processing load (Lenzenweger et al 1991; Nuechterlein and Dawson 1984; Rund and Landrø 1990). The deficit is composed of a low sensitivity and a low target stimulus response rate - but not a low response criterion - relative to that of normal individuals. Characteristically, the low sensitivity is global: that is, there is no evidence of a greater reduction of sensitivity in predisposed subjects compared to controls over time (Lenzenweger et al 1991; Nuechterlein and Dawson 1984).

There are several possible interpretations of the observed CPT deficits. The most prominent are the following:

1. CPT deficits might relate to a general dysfunction; e.g. reduced processing capacity/attention. This interpretation could explain the observed difference between schizophrenic patients and "boundary individuals" respectively. Thus it is possible that the decompensated schizophrenics lack more processing resources than the compensated "boundary individuals".

2. In continuation of the above, it might also be a possibility that tasks with a low processing load involve relatively automatic, passive cognitive processes, while tasks with a high processing load involve controlled, capacity/attention demanding processes. So saying, "boundary individuals" might only reveal a deficit in the controlled, capacity demanding processes - the vulnerability indicator - whereas schizophrenics might have an additional deficit in the relatively automatic, passive processes (Nuechterlein and Dawson 1984).

3. The fact that the observed reduced sensitivity is global rather than time-dependent could make probable other explanations for the deficit. If the deficit in question is actually a reduced ability to sustain attention, a significant reduction of sensitivity over time would be expected. As this is not the case, the CPT - even though it demands sustained attention - might reveal a vulnerability indicator of quite a different nature; e.g. a sensory or perceptual deficit (Nuechterlein et al 1994). Nuechterlein and colleagues (1994) tried to subject the possibility to a critical examination. They applied two different research set-ups on a patient population of medicated schizophrenics - tested in both an active psychotic stage and in remission - and on a control population of normal individuals.
   In one research paradigm they wanted to assess the relevance of early perceptual processes for the CPT deficits, using a perceptually degraded target stimulus. The finding of low sensitivity in patients was interpreted as expressing that an abnormality in the early visual information processing is a stable vulnerability indicator. Green & Nuechterlein (1999) suggested that the sensory-perceptual abnormality observed in the CPT is analogous to the one reflected in Visual Backward Masking. In the second research paradigm, Nuechterlein and colleagues (1994) wanted to asses the importance of short-term (working) memory to CPT deficits, using a target stimulus composed of a sequence of two numbers. A significant deficit of sensitivity was observed in both psychotic and remitted schizophrenic patients - the latter, however, less pronounced. As the deficit was neither independent of the clinical state nor normalised in remitted patients, it could not be classified as a stable vulnerability indicator or as an episodic indicator. Instead, a new phrase was introduced: *a mediating vulnerability factor.* This relates to a deficit which on the one hand is constantly present, reflecting vulnerability for schizophrenia, and on the other is dependent of the clinical symptoms of the patients (Green and Nuechterlein 1999; Nuechterlein et al 1994)

Span of Apprehension

Span of Apprehension (SOA) is an experimental paradigm which tests the immediate span for stimuli, i.e. the number of stimuli that can be attended to, apprehended and reported in a single brief exposure. Numerous different forms exist. The subject may simultaneously be presented for an array of test stimuli for 50-100 msec. In the "forced choice partial report version", the one most often used, the individual has to report which explicit target stimulus (e.g. "t") of two target stimuli (e.g. "t" and "f") is contained in the array of non-target stimuli (other letters, the number of which is increased during the task).

There is substantial empirical evidence for SOA deficit in "spectrum individuals" (Braff 1993; Nuechterlein and Dawson 1984; Rund and Landrø 1990; Siegel 1995). Patients exhibit poor capacity to identify the target stimulus as the array of letters exceeds 10 (Siegel 1995). Specificity for the schizophrenic spectrum has been supported by the fact that schizophrenics exhibit a poorer ability to identify target stimuli than do non-psychotic psychiatric patients and normal controls (Nuechterlein and Dawson 1984). A problem, however, is insufficient data on the performance of non-psychotic psychiatric patients compared to normal controls. Provided that these patients do not perform significantly poorer than controls, it is reasonable to assume that the deficit is specific for schizophrenia. An impaired task-performance in non-psychotic psychiatric patients would, on the other hand, indicate that the deficit is more or less related to psychopathology. Another possible source of error is that the observed better performance of non-psychotic psychiatric patients relative to schizophrenics is the result of a diagnostic unspecific state-marker. Anyway, disclosure of SOA impairments in "boundary individuals" including schizotypals (Braff 1993; Rund and Landrø 1990; Siegel 1995) advocate strongly for these deficits as stable vulnerability indicators for schizophrenia. This has been further supported by the fact that SOA deficits are stable in partly remitted schizophrenic patients (Nuechterlein and Dawson 1984; Rund and Landrø 1990). Moreover, the latter finding excludes that the deficit is an episodic or symptomatic indicator.

Analogous to Visual Backward Masking and CPT the observed deficit can be interpreted as reflecting a specific sensory-perceptual dysfunction or/and a general compromised attentional function:

1. It is possible that the SOA task is a measure of the ability to store information in the sensory memory and transform the information to the short-term memory (Nuechterlein and Dawson 1984; Rund and

Landrø 1990) (fig. 1). In this way, the deficit might be related to a low perceptual sensitivity to discriminate between simultaneously presented target and non-target stimuli, and/or related to slow processing of the information in the sensory memory. This hypothesis is in accordance with the sensory-perceptual interpretation of deficits in Visual Backward Masking.

2. Another possibility is that SOA deficits are the result of various forms of attentional dysfunctions. First, a delayed start of the attentional process would - as a result of informational decay in the sensory memory as early as after 250 msec - markedly handicap the test individual when a fast response is required (Siegel 1995). Second, an inappropriate resource/attentional allocation to irrelevant rather than relevant stimuli might cause SOA deficits. Third, a reduction in available attentional resources combined with a high processing load task, would take up such a great proportion of the resources that few would remain available for other processes, e.g. scanning of the sensory memory, identification and reporting of target stimulus (Siegel 1995).

Reaction time

Reaction time (RT) paradigms involve quantifying reaction time by means of tasks demanding fast responses. The subject is presented for a preparatory stimulus and a target stimulus respectively, separated by a 1-25 sec interstimulus interval referred to as the preparatory interval (PI). The preparatory stimulus prepares the task individual to press a response button as soon as the target stimulus is presented. Two different variables can be manipulated: the length of the PI and the modality of the stimulus, respectively. A simple research paradigm is to present the target stimulus with varying PIs - regular/predictable and irregular/unpredictable - of a given length. In another research paradigm, the modality of the preparatory stimulus as well as of the target stimulus alternate: that is to say, they can have the same modality (e.g. auditive-auditive) or different modalities (cross modality conditions, e.g. visual-auditive).

Compared to normal controls, patients in the schizophrenic spectrum generally show a longer RT and a deficiency in the ability to profit from regular PIs under simple research paradigms, and impaired response at cross modality conditions (Braff 1993; Chapin et al 1987; Nuechterlein and Dawson 1984; Rund and Landrø 1990; Siegel 1995).

A generally longer RT compared to normals is described in "boundary individuals", schizophrenics and multiple other diagnostic groups including brain-damaged patients and some depressive patients (Nuechterlein and Dawson 1984; Rund and Landrø 1990). The same phenomenon is described in normal individuals brought up by a schizophrenic parent (Nuechterlein and Dawson 1984). Regarding "boundary individuals" the results are, however, inconsistent (Nuechterlein and Dawson 1984; Rund and Landrø 1990). Impairment in RT meets some of the conditions for a vulnerability indicator: It has been demonstrated in schizophrenics compared to normals, and is disproportionately represented in first-degree relatives of these patients. The presence of the deficit in other groups of patients and normals raised by schizophrenics, do not, however, support the idea of this deficit as an explicit stable vulnerability indicator or trait marker for schizophrenia. This is further emphasised by the fact that the deficit has been found to correlate with hospitalising among schizotypals, schizophrenics, major depressive and borderline personality disordered patients (Chapin et al 1987). That is to say, the deficit actually might result from psychopathology per se or/and environmental factors related to psychopathology.

Characteristically, normals display a faster RT when the target stimulus is preceded by regular/predictable PIs instead of irregular/unpredictable PIs. The ability to profit from regular PIs is lost in most remitted as well as in acutely ill schizophrenics when the PI exceeds 2-6 sec. At these conditions patients actually perform better - show a shorter reaction time - at irregular PIs than at regular PIs (Rund and Landrø 1990).

The crossover effect has also been shown in some "boundary individuals", in a small group of bipolar affective patients, in patients with lesions of the temporal lobes and, to a lesser extent, in certain older normals (Nuechterlein and Dawson 1984; Rund and Landrø 1990; Chapin et al 1987). The contemporary presence of the crossover effect in schizophrenics independent of their clinical state, and in "boundary individuals", and the absence of the crossover effect in normals, render the crossover effect/the deficit a probable vulnerability indicator for schizophrenia. This is irrespective of the above mentioned lack of diagnostic specificity, which, anyway, has been doubted by Chapin and colleagues (1987). They found an identical crossover deficit in schizotypals and schizophrenics but did not observe significant differences in performance amongst major depressive, borderline personality disordered patients and normals. These observations contradict the opinion that the deficit is a result of psychopathology per se.
Impaired reaction at cross modality conditions (modality shift effect) has been shown in schizophrenics (Braff 1993; Nuechterlein and Dawson 1984; Siegel 1995) and in major

depressive patients (Nuechterlein and Dawson 1984), but not in first-degree relatives of schizophrenics. Lack of evidence concerning schizotypals, remitted schizophrenics and other patient groups makes it impossible to deduce whether the deficit is a consequence of a genetic predisposition or of psychoses or psychopathology per se.

The crossover effect - the RT deficit, which possibly represents a stable vulnerability indicator for schizophrenia - might be related to a shortness of continuous attention or an inconsistency of attention (Braff 1993; Rund and Landrø 1990). Such a dysfunction would prevent the patient from taking advantage of the regular PI, because the preparatory stimulus is temporally so far from the target stimulus that the attention is unable to continuously register both stimuli. Nuechterlein & Dawson (1984) take a step further and suggest that the deficit is related to a lack of ability to maintain conscious capacity-requiring attention - this because conscious attention hypothetically is characterised by an ability to profit from predictable stimuli. However, as the crossover effect actually results in longer RT at regular PIs compared to irregular PIs, Nuechterlein & Dawson state that loss of ability to profit from predictable stimuli cannot be the full explanation for the phenomenon.

The modality shift effect - that may be verified as a stable vulnerability indicator in the future - has been interpreted as reflecting an inflexibility of attention (Braff 1993): that is, an attentional perseverance that fixes the attention in one modality, by means of which attentional shifts between various modalities is compromised.

Prepulse inhibition of the startle response and P50 gating

The term gating refers to the part of the information processing that is involved in the initial screening of stimuli, selection of relevant stimuli and inhibition of irrelevant stimuli (Braff 1990). This sensory filtering mechanism or buffer capacity is central to the ability to integrate sensory data in order to prevent the system from breaking down as a consequence of overload (Andreasen 1997; Carlsson 1988; Glenthøj et al 1997; Glenthøj and Hemmingsen 1999). There are two major methods by which sensory-motor gating can be measured, "Prepulse inhibition (PPI) of the startle response" and "P50 gating" (Braff 1993).
To elicit the startle response in PPI, a relatively strong auditory or tactile stimulus is presented. The eye blink component of the startle response is measured by the electromyographic response of the orbicularis oculi muscle. PPI is assessed by presenting a week prestimulus 30-500 msec before the startling stimulus and measuring the resulting reduction, or PPI, of the startle response. This passive research paradigm can be made active - that is, the initial weak stimulus can change according to pitch; some pitches are decided in advance to be relevant and irrelevant respectively; and the task individual is instructed to focus on the relevant, initial stimuli only.

In passive research paradigms involving 30-500 msec ISIs, the weak stimulus normally inhibits the ability of the strong stimulus to evoke a startle reflex, i.e. the amplitude of the startle reflex is blunted or attenuated by the prepulse (smaller blinks). The phenomenon is intra-modal and cross-modal and seen in most mammals (Braff 1993; Braff et al 1992; Dawson et al 1995). Chronic medicated schizophrenics and "boundary individuals" show a significantly poorer PPI compared to normals at short ISIs (Braff 1993; Braff et al 1992; Dawson et al 1995). Analogue deficits have been observed in patients with OCD and Huntington disease and in children afflicted by nocturne enuresis. In passive research paradigms involving stimuli of the same modality and ISIs greater than about 1000 msec, normal individuals do not show PPI, but rather facilitation of the startle response (Dawson et al 1995).

When active research paradigms are implemented, normals show a relatively greater PPI at ISI of 120 msec - but not at ISI of 60 msec - and a relatively greater facilitation at ISI of 2000 msec, when the initial weak stimulus is relevant compared to irrelevant (Dawson 1990; Dawson et al 1995; Nuechterlein et al 1994). Remitted schizophrenic patients do not show a reinforced PPI at active experimental conditions, and relatively asymptomatic schizophrenic patients in the early stages of the disease show neither reinforced PPI nor reinforced facilitation when the initial stimulus is relevant (Dawson et al 1995; Nuechterlein et al 1994). Patients, on the other hand, do not perform differently from normals when the initial stimulus is irrelevant. Analogue, or even more pronounced, deficits are seen in high-risk individuals defined by a tendency towards perceptual disturbances and magical thinking (Dawson et al 1995).

As defective gating/PPI has been revealed in both passive and active research paradigms in both relatively asymptomatic, chronic and remitted schizophrenics, and in "boundary individuals", this deficit probably represents a stable vulnerability indicator or trait-marker for schizophrenia. As longitudinal studies of sensori-motor gating in drug-naive schizophrenic patients before and during treatment with antipsychotics are still missing, it is not as yet possible to come to a valid conclusion regarding the effect of antipsychotic drugs on PPI of the startle reflex. Preclinical studies, however, point to an influence of

antipsychotics (see Glenthøj et al 1998 or Glenthøj and Hemmingsen 1999); if this is also the case in patients, the deficit must instead be characterised as a mediating vulnerability indicator. Another problem is the finding of reduced PPI in OCD and Huntington patients. The deficit in these patients might be a consequence of dysfunction of the same brain areas/transmitter-systems as in schizophrenics. Thus, these observations are not inconsistent with a genetically associated PPI deficit in "spectrum individuals" - however, they warn that the task is not specific.

P50 gating is an auditive two-stimulus conditioning task based on cerebral event-related potentials (ERPs): that is, cerebral electric activity evoked by a stimulus. An initial conditioning stimulus and a following test stimulus is presented in a close temporal sequence separated by an ISI of 500 msec. Each stimulus evokes cerebral electric activity: for instance, a positive wave (P50) about 50 msec following each stimulus-presentation. This can be quantified by means of frontal, central and/or parietal electrodes.

Several studies have demonstrated that when two rapid-click stimuli are separated by 500 msec, the P50 ERP response to the first (conditioning) stimulus is always fairly large, whereas the P50 response to the second (test) stimulus is attenuated in normal individuals (Braff 1993). This reflects the fact that the first stimulus protects the individual against sensory overload by inhibition or gating of the effect of the second stimulus (Braff 1993; Braff et al 1992; Judd et al 1992). In both medicated and non-medicated schizophrenics, and in "boundary individuals", this inhibitory process is compromised, reflected in a relatively greater P50 following the test stimulus (Braff 1993; Braff et al 1992; Judd et al 1992). These observations support the opinion that defective gating is a vulnerability indicator for schizophrenia. One study (Judd et al 1992), however, points to a modest effect of treatment on the deficit. If this is the case, loss of gating is only a mediating vulnerability indicator. That impairment of gating is a mediating vulnerability indicator has also been supported by the fact that manic patients in the acute phase demonstrate defective P50 gating (Judd et al 1992). In these patients the task-result is normalised following remission. The finding in manic patients does not contradict the opinion that the dysfunction is a result of a genetically determined vulnerability, but it does, again, call for circumspection when it comes to the specificity.

An important question is which element(s) of information processing is or are involved in gating in normals and which are dysfunctional in "spectrum individuals". In clinical trials, defective PPI gating has been found to be coherent not only with dysfunctional P50 gating, but also with lateralised attention, distraction and working memory; functions related to the temporo-limbic region as well as prefrontal cortex (Braff 1993; Braff et al 1993; Karpre et al 1996). Furthermore, it has been observed that by changing the ISI in PPI, the regions in the brain activated in functional magnetic resonance (MR) change. A disturbed attentional function might result in the disturbances mentioned above. Accordingly, lesions of the relatively automatic, involuntary, preattentive attentional processes and/or the controlled, voluntary, attentive attentional processes have been proposed as candidates for an underlying dysfunction (Braff 1993; Dawson 1990; Dawson et al 1995; Nuechterlein et al 1994). In light of the above-mentioned findings, it is possible that passive research paradigms including short ISIs involve automatic processing of the initial stimulus - the gating effect is present in normals even though they are not requested to attend the initial stimulus.

When it comes to the active research paradigms, it is likely that ISIs above 120 msec involve controlled processing of the initial stimulus - both gating and facilitation of the initial stimulus are reinforced when the initial stimulus is relevant and thus demands focal attention. The fact that the gating effect is not reinforced at ISIs of 60 msec indicates, however, that also automatic processing of the initial stimulus is involved at active research paradigms (Dawson et al 1995).
Interpreting the deficits of the "spectrum patients" in the light of the above-mentioned hypotheses, the results are, to a certain extent, inconsistent: the passive research paradigm illustrates dysfunctioning automatic attentional processes in patients, whereas the active research paradigm illustrates dysfunctioning controlled attentional processes, but intact automatic processes - patients do not perform any differently from normal individuals when the initial stimulus is irrelevant. The last-mentioned, together with previously described trait-connected deficits in CPT and RT, strongly advocate that only a deficit in controlled attentional processes is a trait-marker.

Conclusion

Cognitive deficits in patients in the schizophrenic spectrum are recognised in several tasks; Visual Backward Masking, CPT, SOA, RT, Prepulse inhibition of the startle reflex and P50 gating, respectively. The deficits are observed in schizophrenics in acute psychotic episodes and in remitting episodes, in first-degree relatives of schizophrenics and in schizotypals. Accordingly, it is likely that they represent stable or mediating vulnerability indicators or trait markers for schizophrenia. In

other words, the previously described information processing and attentional dysfunctions, which hypothetically determine the observed deficits, reflect a genetic predisposition to schizophrenia - perhaps the "core" of the schizophrenias.

The above-mentioned assumption, combined with the fact that the schizotypal symptomatology resembles the schizophrenic with the important exception that schizotypal individuals rarely become psychotic, supports the following hypothesis: The schizotypal, compensated individual possesses a genetically linked information processing and attentional dysfunction that is reflected in the characteristic symptomatology, while schizophrenic, decompensated individuals have additional deficits determined by other genetic and environmental stressors. This is reflected in a more severe symptomatology.
The fact that cognitive deficits or information processing and attentional dysfunctions can be characterised as both stable or mediating vulnerability indicators and as episodic or symptomatic indicators is not necessarily inconsistent. It is likely that only certain parts of dysfunctioning attentional function and impaired information processing are linked to a genetic predisposition to schizophrenia. Exactly which parts are concerned can be approximated by an analysis of the deficits in the above-mentioned cognitive tasks, which aim to deduce common features of the relevant information processing and attentional dysfunctions.

Obvious common features - candidates for stable vulnerability indicators or trait markers - are specific sensory-perceptual dysfunctions; dysfunctions localised to a certain stage in the processing of information, and/or a general attentional dysfunction: i.e. a dysfunction involving the information processing cascade as a whole.

As regards sensory-perceptual dysfunctions, Visual Backward Masking, CPT and SOA all point to a reduced rate of information processing in sensory memory (see fig. 1) and/or a reduced perceptual sensitivity. An important point concerning the rate of information processing is, however, that the results on Visual Backward Masking could also suggest a general rather than a specific or localised reduced rate of information processing. The latter interpretation seems quite the most confident. First, it supports the idea that the rate of information processing in the sensory memory is reduced. Second, the above-described cognitive tasks might only enable one to make deductions concerning the early part of the information processing. That is to say, other cognitive tasks could reveal a reduced rate of information processing in the later parts of the information processing cascade as well - e.g. encoding and retrieval of information from long-term memory via short-term memory. Apparently, the demonstration of a normal response criterion in "spectrum individuals" in the CPT could argue against a reduced perceptual sensitivity in these patients. Thus, one could expect that individuals characterised by reduced perceptual sensitivity would exhibit a high response criterion. It is, however, important to mention the possibility that "spectrum-patients" might show a normal response criterion despite a reduced perceptual sensitivity, simply because these individuals are characterised by a tendency toward a fast and rash deduction.

Regarding disturbed attentional function, a common feature is a reduction in the amount of attentional resources that the "spectrum-individual" has to allocate to test-relevant cognitive processes. This is concordant with the assumption - emphasised in relation to the discussion of results on the CPT, RT, PPI of startle response and P50 gating - that controlled, capacity-restricted, attentive attentional processes are compromised in "spectrum individuals". It is imaginable that the phenomenon is determined by inappropriate allocation of resources to task-irrelevant rather than task-relevant stimuli (see section on CPT and SOA). Apparently, the possibility that relatively automatic, not capacity-restricted, preattentive processes are defective too (see section on CPT, PPI and P50 gating) is not consistent with the above-mentioned. This defect might not, however, reflect a genetic predisposition to schizophrenia, but rather other genetic and environmental stressors. Thus, in the section on CPT it was assumed that only decompensated schizophrenics have defective automatic, not capacity-restricted, processing. In agreement with this, it is likely that the schizotypals that showed dysfunctioning automatic attentional processes in the two passive gating research paradigms do not make up a representative selection of "boundary individuals", but rather a more diseased subgroup. That is to say, schizotypal patients that eventually develop schizophrenia might be over-represented in this group relative to their representation in the total population of "boundary individuals". The correctness of this assumption could be clarified by means of a cohort investigation assessing the potential development of schizophrenia in schizotypals that show deficits in passive gating paradigms.

Apparently, a picture emerges of a sensory-perceptual dysfunction on the one hand, and a reduced amount of attentional resources to test-relevant processes on the other. The causal connection is as yet unknown; one alternative is that the dysfunctions have an undefined cause in common, another that one of the

dysfunctions determines the other. Starting from the latter, it is thus possible that a reduced perceptual sensitivity causes an erroneous early information processing and interference between relevant and irrelevant perceptual data. The result would be an excessive use of attentional resources and, with that, reduced attentional capacity for the task-relevant cognitive processes. Conversely, it is also possible that a generally reduced amount of attentional capacity for task-relevant cognitive processes results in compromised information processing, or sensory-perceptual dysfunction.

In conclusion, cognitive tasks and models on information processing and attention are useful tools for achieving a greater understanding of the schizotypal state and its relation to the schizophrenic spectrum. That is to say, this approach - on the one hand empirical, on the other speculative - can be considered an important, heuristic step on the way to clarification of the schizotypal psychopathology.

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REVIEW/MINI-REVIEW ▸

Stress, Depression and the Activation of the Immune System

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Summary

Both stress and depression have been associated with impaired immune function and increased susceptibility of the patient to infectious diseases and cancer. While it was initially thought that the hypercorticosolaemia caused a suppression of immune function, it is now apparent that adaptive changes result from chronic stress and depression that lead to a hypoactivity of the glucocorticoid receptors on immune cells and in limbic regions of the brain. Thus depression is now thought to be associated with activation of some aspects of cellular immunity resulting in the hypersecretion of proinflammatory cytokines and the hyperactivity of the hypothalamic-pituitary-adrenal axis. There is also experimental evidence to show that such immune activation induces "stress-like" behavioural and neurochemical changes in rodents which supports the hypothesis that the hypersecretion of proinflammatory cytokines are involved in the pathology of depression. This review attempts to show how the immune, endocrine and neurotransmitter systems are integrated and how the result of such integration may be causally involved in the aetiology of depression.

Key words: *depression, chronic stress, proinflammatory cytokines, prostaglandins, glucocorticoids.*

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Introduction

The concept of an inter-relationship between the psychological state of a depressed patient and the immune status can be traced back to Galen who, in 200 AD, suggested that melancholic women are more susceptible to breast cancer than sanguine women (Leonard 1987). Over the past 15 years it has become apparent that the central nervous system (CNS) and the immune system are intimately connected and that a functional bidirectional communication exists between these systems (Ballieux 1992). Indeed, it may be possible to conceive of the nervous, endocrine and immune systems as being part of a single integrated network rather than three separate systems. The study of the interactions between these systems has given rise to the new discipline of psychoimmunology, a term first coined by Ader, Felten and Cohen in1987.

It is widely accepted that stress and psychiatric illness can compromise immune function (Leonard 1990). Furthermore, soluble mediators released by immune cells can influence brain function and cause changes in behaviour in both man and lower animals. In addition to the behavioural changes that occur in depressed patients, there are also profound alterations in the endocrine and immune systems (O'Connor and Leonard 1998). Most of the initial studies of the immune changes in depression indicated that a suppression of immune function occurs as indicated by an impaired zymosan induced neutrophil phagocytosis (O'Neill and Leonard 1990), mitogen-stimulated lymphocyte proliferation (Kronfol and House 1989) and natural killer cell (NKC) activity (Irwin et al 1992).

In addition to the immune changes that occur in depressed patients, a number of studies have concentrated on indices of immune function in those who have been exposed to stressful life events such as bereavement, divorce and academic examinations. Exposure to such stressful events has also been reported to cause impairment in various aspects of cellular immune function that qualitatively resemble those changes reported to occur in depression (Irwin 1995).

Despite these changes demonstrating that immunosuppression occurs in those exposed to psychological stress or to depression, there is also evidence that activation of some aspects of

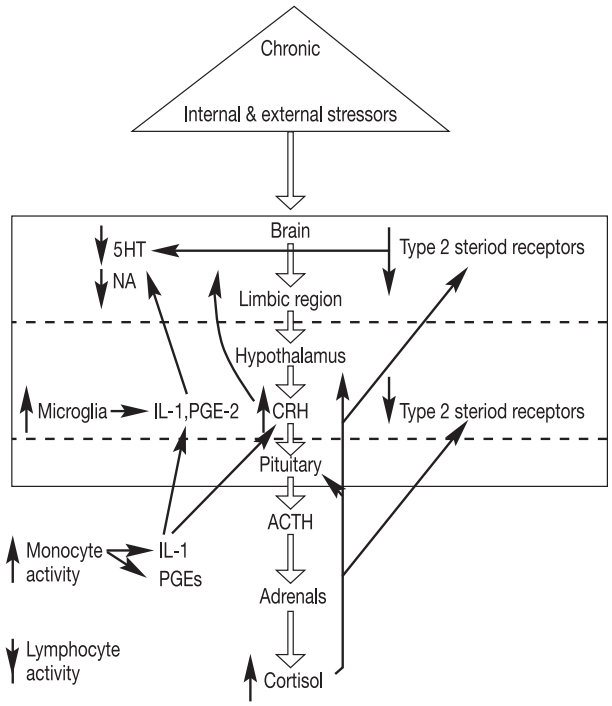
the immune system can also arise (Maes et al 1995). This serves to emphasise the complex interrelationship that exists between external or internal stressors, activation of the pituitary adrenal axis and the subsequent changes in immune function.

The purpose of this review is to present the evidence that implicates the proinflammatory cytokines as the causal factors in depression and in the impact of stress that may trigger the onset of depression.

CNS-Immune interactions: a bidirectional pathway

Interactions between the brain and the immune system may occur through the direct innervation of lymphoid compartments by the sympathetic nervous system, by the release of peptides and other mediators from paracrine cells or by hormones. Various forms of stress have long been known to affect immune function but it is less well known that immune challenges can also affect both behaviour and brain function. For example, proinflammatory cytokines such as IL-I, IL-6 and tumour necrosis factor alpha (TNF alpha) that are released from activated macrophages in event of a bacterial or virus infection, are known to increase slow wave sleep, decrease the blood glucose concentrations, induce malaise and fatigue and cause a lowering of mood (Dantzer and Kelley 1989).

There is also evidence that immunization causes a change in the catecholamine content of lymphoid tissues and the hypothalamus (Besedovsky et al 1985). Such actions result in functional changes in the hypothalamus as exemplified by an increase in the firing rates of hypothalamic neurons in rats following an antigen challenge (Besedovsky et al 1985). From such observations it has been argued that the immune system may act as an afferent sensory organ for the central nervous system (CNS) providing it with information that arises in the periphery in response to the immune changes that occur following an antigen challenge (Blalock and Smith 1985). Consistent with this view is the observation that sheep infected with intestinal parasites show differences in exploratory behaviour from those that have been immunised against such parasites (Gates et al 1992). A diagrammatic representation of the relationship between the immune, endocrine and neurotransmitter system is shown in Figure 1.



Interrelationship between the brain, immune and endocrine systems in depression

(leonard, 1994)

LEGEND

CRH = corticotrophin releasing hormone
IL-1 = interleukin 1
ACTH = adrenocorticotrophic hormone
PGE2 = prostaglandin E2

Figure 1

Stress and the immune system

Because stress activates both the hypothalamic-pituitary-adrenal-axis (HPA axis) and the sympathetic nervous system (SNS), it is not surprising to find that most acute stressors can modify the immune response. It is well known that plasma catecholamines released from the adrenals in response to stress, in addition to the adrenal glucocorticoids, can cause immuno-suppression. There are numerous experimental studies showing that various types of externally applied acute stressors (for example, electric shocks, social defeat, maternal separation, immersion in cold water) suppress some aspects of immune function. Similarly chronic stressors such as overcrowding have been shown to suppress aspects of cellular and humoral immunity. Indeed, it is difficult to consider any aspect of cellular and humoral immunity that is not altered by some stressor (Maier et al 1994).

It is evident from the results of both the experimental and clinical studies of the effects of stress on the immune system that all stressors do not produce identical changes in the immune and endocrine systems. It has long been known that different stressors produce different degrees of SNS and endocrine activation (Mason 1971). For example, one stressor might strongly activate the SNS but have relatively little effect on the HPA axis whereas another may have the converse effect. In addition, the time course of these changes will differ for different stressors and for the psychological state of the individual. Moreover coping strategies are important in that the individual can learn to modify the adverse

impact of the stressor (Mormede et al 1988). It must also be emphasised that the specific immune response involves a complex cascade of events that may extend over several days. As the catecholamines, endorphins, glucocorticoids, etc. play crucial roles in modulating this cascade, the effects of stress will, of necessity, be variable. Thus experimental and clinical situations will arise in which stressors may have an effect, have no effect or even an enhanced effect on immune function (see Croiset et al 1987).

Fleshner and co-workers have shown, for example, that a stressor will interfere with antibody synthesis, determined several weeks following the antigen administration, only if the stressor is applied near the time of the antigen exposure (Fleshner et al 1995). Such findings serve as a caution in extrapolating from studies that have determined one aspect of immune function at one time point only from which conclusions are drawn that stress suppresses immune function. Many immune parameters are non-specific and assess some intermediate aspect of the immune response (for example, the synthesis of the interleukins or proliferative response of T-cells to mitogens) rather than an effector end point that detects and destroys antigen, recognises virus infected cells, etc. It must be remembered that the immune system contains a high degree of redundancy and therefore the changes in part of the immune cascade are not by themselves evidence that the final end point of the immune process (for example, the production of a specific antibody) is affected (Cunnick et al 1991).

There is a large and relatively consistent literature on the effects of stressful life events on predisposition to both physical illness and infections. While the correlations between such life events and illness are not large, generally accounting for only about 10% of the variance (Weisse 1992), the effects are consistent across populations and different types of life events.

Bereavement stress has been the subject of several important studies. There is also evidence that risks to health associated with separation and divorce are greater than with bereavement (Kiecolt-Glaser et al 1987). For example, Kiecolt-Glaser et al (1987) showed that separated or divorced women had a poorer immune function on five of the six immunological variables studies than matched married women. Somewhat similar findings were reported for separated or divorced men (Kiecolt-Glaser and Glaser 1988). It should be emphasised that the sample sizes in these studies was quite small, but such data does serve to emphasise the impact of severe life events on the immunological state and consequence health of normal individuals.

The effect of chronic stress on individuals caring for patients with Alzheimer's disease has also been the subject of several studies. It has been shown, for example, that such individuals show a high risk of depression (Crook and Miller 1985; Fiore et al 1983). In addition to the greater physical and emotional distress shown by the carers, there is also evidence of impaired immune function (Kiecolt-Glaser et al 1991). Other studies of those individuals subject to chronic environmental stress (for example, living in the vicinity of Three Mile Island in the USA, the site of a nuclear power plant accident some years ago) showed that the residents had fewer T-suppressor cells, B-lymphocytes, and natural killer cells than a comparable group living in a normal environment (Davidson and Baum 1986). The conclusions of these studies is that chronic stress in man does not necessarily lead to immunological adaptation.

Clearly, there are marked differences between the stress induced changes in rodents and those reported in man. Thus, in rodents, acute stress appears to be immunosuppressive, whereas chronic stress is associated with adaptive changes or even enhancement of the immune response (Cohen and Crnic 1982; Monjan and Collector 1977).

Examination stress in university students has been the subject of several studies in the United States. Thus, a decrease in natural killer cell number and function has been reported by several groups of investigators (Glaser et al 1996), effects that were not attributable to poor nutritional status. In addition, academic stress has been associated with significant changes in antibody titers to latent herpes viruses suggesting changes in cellular immunity. In particular, elevated antibody titers to the Epstein Barr virus (the causal agent for infective mononucleosis), herpes simplex virus type 1 (that causes cold sores), and cytomegalovirus (which causes the monucleosis syndrome) were raised prior to examinations but returned to normal levels following the examination (Glaser et al 1985). There were additional changes in mitogen stimulated lymphocyte replication associated with academic stress. Thus, the incidence of self-reported infectious illness was also increased in these individuals. The effect of relaxation techniques on these immune parameters was also studied and showed that although the percentage of helper T-cells did not decline so markedly in those subjects that were given relaxation exercises, natural killer cell activity was unaffected by such an intervention. It may be concluded from these studies of the effects of stress and adverse life events that adaptive changes in the immune system are not pronounced in man.

One of the major problems arising from the clinical studies lies in the difficulty in

adequately defining stress, because the same event may have different effects on different individuals. Furthermore, most of the components of the immune system normally vary within wide limits, thereby making the small, but important changes difficult to detect. Added to these problems is the difficulty in deciding which parameter accurately reflects the true status of the individuals immune defences.

Interaction between the brain and immune system in stress and depression

The monoamine hypothesis of depression proposes that a deficit of brain noradrenaline (NA) and/or serototonin (5-HT) may be causally involved in the symptoms of illness (Baldessarini 1975). Another theory of depression suggests that the disorder in hypothalamus-pituitary- adrenal (HPA) axis causes an increase in secretion of corticotropin-releasing factor (CRF), which stimulates adrenocorticotrophin hormone (ACTH) and cortisol release (Bateman et al 1989). Recently, the macrophage theory of depression, which will be discussed in detail later in this review, has also been proposed. In this hypothesis, the abnormal secretion of some cytokines such as interleukin-1 (IL-) and interferon-alpha (INF-alpha), results in disordered secretions of CRF, ACTH, prolactin, and cortisol, together with a depressive state (Smith 1991). These three hypotheses may be linked. Whatever changes in the central nervous system (CNS) or in the endocrine system occur, different aspects of immune function are affected. It is known that noradrenergic and cholinergic terminals innervate the thymus gland and bone marrow and there are different neuropeptide, neurotransmitter and hormone receptors on lymphocytes and monocytes. In addition, cytokines produced by immune cells and microglia exert different effects on the brain and on the endocrine and immune systems (Bost 1988; Farrar 1988).

A number of studies have shown that stress and depression are often associated with an impairment in immune function (Kronfol and House 1989). At the cellular level, a reduction in mitogen-stimulated lymphocyte proliferation and neutrophil phagocytosis and elevated monocyte activity has been reported in stress and depression (Leonard 1990; McAdams and Leonard 1993; O'Neill and Leonard 1990). An increase in total white cell number and an abnormality in differential white blood cell (WBC) count (for example, increase in the percentage of neutrophil and decrease in lymphocytes) has also been found after stress or in depressed patients (Maes et al 1992). Recently, leucocyte adhesiveness/aggregation (LAA) has also been reported to be increased during stress; this has been suggested as a marker of stress (Arber et al 1991).

At the subcellular level, it has been reported that serum and plasma concentrations of immunoglobulin (Ig) complement (C) and acute phase proteins are changed in depressed patients (et al; Kronfol and House 1989; Maes et al 1992). For example, IgA, IgM, complement C3, C4 and positive acute phase proteins are increased in depression, while negative acute phase proteins are decreased (Song et al 1994). The concentrations of cytokines IL1, INF-alpha, and tumor necrosis factor are raised and IL-2 is reduced in the depressed patient (Katila et al 1991; Nathan 1987; Smith 1991). At the organ and system level, it has been reported that the weights of thymus gland and spleen are reduced and adrenal is increased during stress (Dohmus and Metz 1991). Histological studies reveal that a stress-induced rise in corticosterone, or an exogenous injection of corticosterone, causes cortical atrophy and lymphocyte necrosis in the thymus gland of rats (Dohmus and Metz (1991). However, despite the circumstantial evidence implicating an interaction between neurotransmitter, endocrine and immune changes, a causal relationship between these changes has yet to be proven.

The macrophage theory of depression

Of all the endocrine changes that are reported to occur in stress and depression, cortisol hypersecretion is the most frequently observed. Although hypercortisolaemia can arise as a consequence of an acute stressor, there is a qualitative difference between the circadian pattern of cortisol secretion in the depressed patient and that observed following exposure to a stressful stimulus. Thus the nadir of the plasma cortisol concentration occurs some 6 hours earlier in the depressed patient than in the stressed, non-depressed patient. The ACTH concentration is also elevated while that of the concentration of corticotorphin releasing factor (CRF) in the cerebrospinal fluid is raised in depressed patients (Linkowski et al 1987; Nemeroff et al 1984). As there is a close association between plasma glucocorticoids and immune function, it is often assumed that the immune changes are a direct consequence of the raised plasma and brain concentrations of the adrenal glucocorticoids. However, this seems unlikely as the prolonged increase in glucocorticoids in depression leads to a decrease in the sensitivity of the CRF and glucocortiocid receptors in the brain, pituitary and on immune cells (Dinan 1994) thereby reducing the inhibitory effect to these steroid hormones on cellular immunity.

What causes the adrenal steroid abnormalities in depression? One possibility is that the elevated proinflammatory cytokine IL-1 is at least partly responsible. It is known that IL-1 has a direct action on the hypothalamus leading the increased release of CRF. *In vitro*,

IL-1 has been shown to stimulate ACTH and growth hormone secretion; these effects are not shared by the other major proinflammatory cytokines, IL6 and TNF alpha. In addition to the direct effect of IL-1 on the HPA axis, there is experimental evidence that macrophages may also secrete ACTH which could directly stimulate the adrenals to synthesise cortisol. Thus an activated macrophage system in depression could both directly and indirectly contribute to hypercortisolaemia.

The question arises regarding the mechanism whereby an increase in peripheral IL-1 can precipitate changes in the immune, endocrine and neurotransmitter systems in the brain. Indeed, an important and unresolved question is whether cytokines released peripherally gain access to the brain in concentrations that are biologically effective.

Cytokines are large hydrophilic molecules (Hamblin 1994), their size and structure being such that passive diffusion across the blood brain barrier (BBB) is likely to be minimal (Hopkins and Rothwell 1995). Currently, it is postulated that cytokines produced in the periphery can act on one or other circumventricular organs, such as the median eminence (ME) and the organum vasculosum laminae terminalis (OVLT) that lack a functional BBB (Hopkins and Rothwell 1995). It has been suggested that cytokines from the periphery bind directly to glial cells on the OLVT, which in turn produce cytokines and other mediators such as prostaglandins, particularly prostaglandin E2 (PGE2).

This hypothesis is consistent with the observations that peripheral IL-beta administration elevates PGE2 concentrations in many brain structures as assessed by *in vivo* microdialysis, which is maximal and most rapid at the OVLT and the medial preoptic area, and that the central increase in PGE2 precedes the onset of fever (Komaki et al 1991). This hypothesis is further strengthened by the fact that many cytokine and endotoxin induced neurochemical (Lavicky and Dunn 1995; Mefford and Heyes 1990) and behavioural (Crestani et al 1991; Hellerstein et al 1989) responses are attenuated by cyclooxygenase inhibitors such as indomethacin. Moreover, certain neurons in the preoptic nucleus have receptors for IL-1, IL-6 and TNF-alpha (Schettini 1990). Finally, it has been reported in rodents that peripheral injection of an endotoxin increases the production of cytokines in the brain. Thus peripheral infections might affect the activity of the human brain at least in part through a similar mechanism (Rivier and Rivest 1993).

Not only does IL-1 act at the OVLT, but it can cross the BBB by an active transport system (Banks et al 1989). For instance, an active transport mechanism for TNF-alpha has been described (Gutierrez et al 1993). The concentration of these cytokines crossing the BBB by such mechanisms may be so low that they are physiologically insignificant (Hopkins and Rothwell 1995), but his may be an important route of entry into the brain when plasma concentrations of cytokines are very high (Banks et al 1989).

In addition to the hypothesis that peripherally produced cytokines affect CNS function via the circumventricular organs, there is also evidence suggesting the existence of neurally mediated mechanisms of communication between peripherally produced cytokines and the CNS (Dantzer 1994). This hypothesis that postulates communication between peripherally produced cytokines and the CNS via a neural afferent pathway is supported by the fact that subdiaphramatic vagotomy attenuates endotoxin induced depressive effects on behaviour, c-fos expression in the CNS and IL-1 beta expression in the hypothalamus (Dantzer 1994). In addition, subdiaphramatic vagotomy has been reported to block HPA-axis activation produced by peripheral IL-I beta and TNF-alpha administration (Fleshner et al 1995) and also hypothalamic noradrenaline depletion produced by peripheral IL-I beta administration.

The findings from the vagotomy studies are important because they indicate that the brain is able to respond to cytokines that have been released at the periphery during the course of an infection or an inflammatory response and to respond to this stimulus by a local synthesis of cytokines. The mechanisms that are responsible for the transformation of the immune message into a neuronal message at the periphery, and the transduction of this neuronal message back into an immune message in the central nervous system, still need to be determined (Dantzer et al 1996; Bret-Dibat et al 1996). Thus, in addition to cytokines produced from microglia and other macrophages within the CNS, peripherally produced cytokines can also affect the brain and produce many physiological, behavioural, endocrine and neurochemical changes following most immunological challenges.

There is now substantial evidence to show that major depression is accompanied by an acute phase protein response, an increased secretion of prostaglandins and by an excessive secretion of proinflammatory cytokines. These and other changes suggest that immune activation may play a role in the pathogenesis of depression and provide the basis for the macrophage theory of depression (Smith 1991). Thus inflammatory cytokines or lipopolysaccharide (LPS) administered to animals or man provoke an extensive set of symptoms that are also

identical to those found in major depression. These changes affect not only the psychological state of the individual but are also associated with changes in the activity of the HPA similar to those seen in depression. There is also evidence that the increase in the circulatory concentrations of IL1 and IL6 mediate the acute phase protein response which is characterised by elevated positive acute phase proteins (Song et al 1994) and a reduction in the serum tryptophan concentration.

The precise mechanism whereby pro-inflammatory cytokines such as IL-1 beta modulate central serotonergic function is uncertain but recent evidence from in vitro studies on JAR cells, components of a choroiocarcinoma cell line derived from human placenta, have shown that IL-1 activates the serotonin transporter directly (Ramamoorthy et al 1995). If a similar effect occurs on central serotonergic neurons, it could result in an increased removal of the amine from the synaptic cleft thereby leading to a reduction in serotonergic function. Receptors for IL-1 beta occur on serotonergic neurons (Cunningham and de Souza 1996) and it is well established that this cytokine is synthesised by neurons and glial cells. Furthermore, raphe neurons may also respond to Il-1 delivered by white blood cells penetrating endothelical barriers during an inflammatory process (Cunningham and de Souza 1996). Thus a reduction in the serum tryptophan concentration associated with elevated acute phase proteins, and an enhanced reuptake of serotonin from the synaptic cleft caused by the action of IL-1 on the serotonin transporter, may contribute to a malfunction of the serotonergic system that is causally associated with depression. Indirect support for this hypothesis comes from the observation that antidepressants suppress the pro-infammatory cytokines (Xia et al 1996). This suggests that the proinflammatory cytokines can act as common mediators for the action of external (for example, psychosocial) and internal (for example, infections and toxins) stressors that are known to play a crucial role in the aetiology of depression.

One advantage of the macrophage theory of depression is that it brings together the disparate changes in the immune, endocrine and neurotransmitter system with the clinical and epidemiological observations and also provides direct predictions that may be tested experimentally and/or clinically. For example, Maes et al (1996) have shown that the concentration of omega 3 fatty acids in the erythrocyte membranes of depressed patients is significantly decreased. This could suggest an imbalance between the omega 3 and omega 6 fatty acid pathway and reflects an increased synthesis of prostaglandins due to the relatively high intake of vegetable oil (a source of omega 6 fatty acids). Thus an increase in omega 6 and/or a decrease in omega 3, fatty acids could contribute to the changes that cause depression. A diet rich in omega 3 fatty acids (fish oil) might therefore have some immuno protective function (Smith 1991; Maes and Smith 1998).

Are changes in immune function causally or coincidentally consequences of stress or depression?

The association between cancer, autoimmune diseases, myocardial infarction, stroke and dementia with depression and the activation of the immune system, particularly involving the proinflammatory cytokines, has been the subject of considerable discussion in recent years. The initial studies indicating that patients suffering from major depression had decreased cellular immune response compared to healthy controls (Kronfol and House 1985; Schleifer et al 1985) helped to lay the scientific basis whereby psychosocial factors could profoundly affect the development of physical and psychiatric disease. However, in well over 30 studies in the last 15 years, the consistency of the immune changes in depression is uncertain, with some investigators findings impaired immunocompetence while others do not. This situation led Miller et al (1993) to review all the published studies regarding the changes in differential white blood cell counts, mitogen induced proliferation of T cells and changes in NK cell activity in depression.
The results of their survey failed to find significant differences between depressives and their controls in the majority of the 30 studies assessed. For example, with regard to mitogen-induced lymphocyte proliferation, approximately half the studies demonstrated a significant decrease in lymphocyte proliferation whereas half the studies found no differences. Finally, of the 10 studies of changes in NK cell activity in depressed patients, 6 reported decreased activity and 4 found no difference. Thus of the 3 parameters of immune function that are frequently evaluated in studies of depression and stress, it does not appear that alterations in the immune system are specific or reproducible correlates of the psychological state, but may be associated with other variables that characterise the patients, such as the age, gender, severity and duration of the stress or depressive episode.

The following factors appear to contribute to the equivocal outcome of the reported changes in cellular immunity in depression.

1. The heterogeneity of the patients used and the controls selected for comparison. In many of the studies cited, the patients were older than their controls and had been hospitalised for several weeks. It is well established that age, gender and hospitalisation status can profoundly affect

the immune status that is frequently not taken into account (Miller et al 1991; Schleifer et al 1989).

2. The variability of the immune assays used. This applies particularly to the mitogen-induced lymphocyte proliferation assay where it has been shown that up to a 50% variability in the results can be obtained in the same laboratory using the same method (Schleifer et al 1989).

3. The relevance of the assays used. The relationship between the number of immune cells, or NKC activity in the peripheral blood, and the competence of the immune system in otherwise healthy individuals is unclear. Given that the immune system is a complex network of multiple cell types with various specialised functions, the number and location of these cells in any one immune compartment of the immune system may not reflect their activity in other compartments (Keller et al 1981). Furthermore, the endocrine and peripheral sympathetic system can vary in their effects on the different immune compartments. For example, while the inhibitory effects of stress on mitogen induced proliferation in the spleen is mediated by catecholamines, in the blood it is mediated by glucocorticoids (Rabin et al 1990).

4. The variation in an immune parameter may be statistically significant between the patients and their controls but still lie within the normal range for immune function. Thus patients may not be immunocompromised from the clinical viewpoint. This could be relevant to the interpretation of the data showing that there is a greater risk of cancer for individuals with high depressive scores (Persky et al 1991). However, further examination of the increased mortality rate in patients with affective disorders indicates that this is due to suicide and accidents rather than to causes related to a disorganised immune system (Martin et al 1985).

5. It is evident that both stressful and non-stressful environmental events can profoundly affect the immune systems. The degree to which stressor can cause suppression of the immune system can be influenced by the perception of the stressful event. Thus there is evidence that the immune system can be classically conditioned (Ader and Cohen 1991). Animals can learn to immunosuppress, or more dramatically immunoenhance, their T-cell, B-cell, NKC and most immune cell functions (Dark et al 1987; Solvason et al 1988). Such factors are frequently ignored in both clinical and experimental studies that seek to explore the relationships between the effects of different types of stress on the immune system.

Conclusions

There are exciting developments relating to the interactions between the immune system and the brain in patients subject to chronic stress or suffering from depression. However, many of the reported studies have concentrated on determining changes in relatively non-specific immune variables in the peripheral blood of those who are otherwise healthy; such findings are therefore conceptually of limited value. The future of psychoneuroimmunology will probably depend on research into the basic physiological processes that underlie the neurendocrine-immune interactions and the relevance of these interactions to the development and outcome of psychiatric illness. Undoubtedly a better understanding of the cytokines, cytokine receptors and their neuromodulators may lead to the development of novel drugs that have psychotropic actions of value in the treatment of mental illness. This could be a most exciting area of neurobiological research in the next decade.

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REVIEW/MINI-REVIEW ▸

A Review of 19 Double-Blind Placebo-Controlled Studies in Social Anxiety Disorder (Social Phobia)

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Summary

Nineteen double-blind placebo-controlled studies on the treatment of Social Anxiety Disorder (Social Phobia) are reviewed. Initial trials yielded a high degree of efficacy for phenelzine, a large difference between drug and placebo and a low rate of placebo response. Controlled studies with RIMAs (moclobemide and brofaromine) yielded more moderate levels of efficacy and more pronounced placebo effects. Results of the Liebowitz Social Anxiety Scale (LSAS) permit a comparison of the outcomes of the different controlled trials. Overall, the reduction in the mean total score with various drugs is inferior to 50%, probably because the chronic nature of the disorder is not amenable to drastic changes in short-term trials. Results with the LSAS and other scales justify a ranking of the efficacy of the drugs: Classical MAOIs > SRIs > RIMAs. Two controlled studies with benzodiazepines (clonazepam and bromazepam) would position them together with the SRIs relative to efficacy but with problems associated with unwanted effects and dependence. Controlled studies with SRIs (paroxetine and fluvoxamine) demonstrated very significant differences from placebo. Paroxetine is the SRI most extensively studied in Social Anxiety Disorder with positive therapeutic results.

Key Words: *Social Phobia, review, drug treatment, paroxetine, moclobemide, sertraline, phenelzine, clonazepam, fluvoxamine, double-blind, placebo-controlled.*

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Introduction

In a cardinal paper, Social Phobia was shown to be a "neglected anxiety disorder" (Liebowitz et al 1985). This situation has changed and 19 randomised double-blind placebo-controlled studies about the pharmacotherapy of Social Phobia have been published. Specific rating instruments to evaluate quantitatively the psychopathology of Social Phobia were developed and applied in the majority of these studies, particularly the Liebowitz Social Anxiety Scale (LSAS). The common methodology augments the interest in comparing results from different studies. Conversely, heterogeneity of clinical presentations, course, comorbidity and other features that may affect treatment outcomes hinder comparisons across studies.

Classical Monoamine Oxidase Inhibitors (MAOIs) (Phenelzine)

Therapeutic effects found in an open study with phenelzine in Social Phobia (Liebowitz et al 1986) coupled with the demonstrated efficacy of MAOIs in atypical depression, a condition associated with "interpersonal hypersensitivity" that is similarly present in Social Phobia (Liebowitz et al 1984), led to the placebo-controlled trial with phenelzine and atenolol in social phobic patients (Liebowitz et al 1992). In an open study the efficacy of tranylcypromine during a one-year treatment of Social Phobia had also been described (Versiani et al 1988).

The double-blind, randomised placebo-controlled study comparing phenelzine to atenolol (Liebowitz et al 1992) comprised a three-phase, 24-week treatment period. From the first acute 8 weeks phase, results of cases treated for more than 4 weeks were analysed. From the second phase, also lasting 8 weeks, a maintenance phase, treatments were further compared after exclusion of non-responders. In the third phase, also of 8 weeks, placebo responders still in the study were excluded while responders to the two drugs were either switched to placebo or continued on the drug until week 24. The double-blind character was maintained throughout the study. Seventy-four patients completed the first 8 weeks phase and at this point the response rates were 64% for phenelzine, 30% for atenolol and 23% for placebo. These response rates differed significantly statistically, the rate of the phenelzine group being significantly superior to the rates of the other two groups. There was no

statistically significant difference between the response rates of the placebo group and the atenolol group. In the second phase of 8 weeks maintenance treatment, patients who had responded kept their gains while moderate responders did not improve further in statistically significant terms. Numbers in the latter category were too small, though. In the third phase of discontinuation 2 out of 6 phenelzine treated patients who were switched to placebo relapsed while 5 who continued on the drug maintained their response. The mean daily dose of phenelzine at the end of week 8 was 75.7 mg.

A second study with identical methodology to the one employed in the trial by Liebowitz et al (1992) compared phenelzine to moclobemide and placebo in primary social phobic patients (Versiani et al 1992) in a similar number of cases, (n=78) and with a similar mean daily dose of phenelzine, of 67.5 mg. In this second study, phenelzine was associated with a very marked response rate already apparent at week 4. In the phenelzine treated patients (n=26) there was not a single non-responder at the end of week 8 whereas 5 and 16 patients were non-responders to moclobemide (n=26) and to placebo (n=26), respectively. The rapid and very marked therapeutic effects of phenelzine in this study may be related to the rapid escalation of the dose. At day 4 of the treatment period most patients were already taking the robust dose of 60 mg/day of phenelzine.

Some similarities between the findings from the pioneer study by Liebowitz et al (1992) and its replication by Versiani et al (1992) with the exception of the atenolol arm being replaced by moclobemide in the second study, are noteworthy. The response rates to placebo were low in the two studies, 25% and 15%, respectively (Table 1). The difference between outcomes assessed with all the rating instruments employed demonstrated a marked effect of phenelzine relative to placebo. In the Versiani et al (1992) study the effect of phenelzine was especially marked with a decrease in the mean Liebowitz Social Anxiety Scale (LSAS) total score of 79% at the end of week 8. At the end of week 16 of the second phase of the treatment period, phenelzine treated patients were almost asymptomatic in the Versiani et al (1992) study, 91% or 19 out of 21 cases who remained until this point meeting the following criteria: CGI (Clinical Global Impressions) score of 1 or 2 plus improvement in the LSAS > 70% plus a Sheehan Disabilities Scale score of 1 or 2. Unwanted effects associated with phenelzine were frequent in both studies and in the Versiani et al (1992) trial there was a very severe hypertensive crisis in one patient, without external explanation (no interaction with drug or food), leading to hospital admission.

In a more recent study, phenelzine was compared to cognitive behavioural group therapy (CBGT), to pill placebo and to educational-supportive group therapy in the treatment of Social Anxiety Disorder (Social Phobia). The results yielded a smaller difference between the response rates of the phenelzine group and the placebo group, not due to a lesser effect of the active drug but because of a larger placebo effect (Table 1) (Heimberg et al 1998).

Reversible Inhibitors of Monoamine Oxidase (RIMAs)

The very positive therapeutic effects of classical irreversible MAOIs, in the treatment of Social Anxiety Disorder led to the study of RIMAs, moclobemide and brofaromine, in the treatment of this condition. If proven efficacious, RIMAs are a far better therapeutic option with a favourable risk/benefit ratio in comparison with the classical MAOIs: less frequent and less severe unwanted effects, no need of a special diet and fewer and less dangerous interactions with other drugs because of the reversibility.

Moclobemide was first studied in the treatment of Social Anxiety Disorder in a placebo-controlled study in comparison with phenelzine in 26 patients out of 78 with a mean daily dose of 580 mg (Versiani et al 1992). The therapeutic effects of moclobemide in this study were less marked than those of phenelzine but were significantly superior to those of placebo, statistically and clinically. Despite the moderate size of the total sample (n=78), the results of the Versiani et al (1992) study were very consistent in discriminating the three treatments relative to the efficacy for the treatment of Social Anxiety Disorder (Table 1). Response rates (CGI = 1 or 2) at the end of the first 8 weeks acute phase of the Versiani et al (1992) study were 85%, 65% and 15% for the phenelzine, moclobemide and placebo groups, respectively (Table 1) and the differences between the three proportions of response rates were statistically significant: i.e. phenelzine > moclobemide > placebo ($p < 0.001$).

In a large multicentre study (n=578), the efficacy and safety of moclobemide for the treatment of Social Anxiety Disorder was determined by comparisons between two fixed dose schedules (300 or 600 mg/day) and placebo. A dose-response curve was found with the results showing the efficacy associated with the 600-mg/day dose of moclobemide to be statistically significantly superior to placebo at weeks 8 and 12 of the treatment period. In the efficacy parameters, the patients treated with the 300-mg/day dose of moclobemide had intermediate results, half of the measures being statistically significantly different from placebo and the other half superior to placebo without

reaching significance levels. The proportions of responders in the three treatment groups, moclobemide 600 mg/day, moclobemide 300 mg/day or placebo were not markedly different, 47%, 41% and 34%, respectively. The difference between the proportions of responders in the 600-mg/day and in the placebo group was highly significant ($p < 0.0003$), though. (The International Multicenter Clinical Trial Group on Moclobemide in Social Phobia, 1997).

Two studies reporting negative results relative to the efficacy of moclobemide in the treatment of Social Anxiety Disorder in comparison with placebo have been published, a rare and welcome occurrence in a world of positive findings in the literature on the pharmacotherapy of psychiatric disorders. Schneier et al (1998) reported very small therapeutic effects both for moclobemide and placebo, 17.5% and 13.5% of responders, respectively, in a 16-weeks trial on the treatment of Social Anxiety Disorder in 77 patients. Schneier et al (1998) did exclude 5 placebo responders after a 1-week, single-blind placebo run-in but this modest exclusion cannot explain the very low rate of placebo response of 13.5%. Schneier et al (1998) did discuss their findings, pointing out that they conformed to the smaller moclobemide/placebo differences found in the International Multicenter Study (1997) with 578 patients and in the large US study by Noyes et al (1997). If one examines Table 1, these points made by Schneier et al (1998) do fit the data neatly, relative to a difference in efficacy in Social Anxiety Disorder between moclobemide and placebo smaller than 20%, assessed by proportions of responders according to the CGI (Clinical Global Impressions) or to decreases in the total score of the LSAS (Liebowitz Social Anxiety Scale). However, it is difficult to explain the difference between the proportion of placebo responders in the Schneier et al study (1998) of 13.5% versus 34% and 32% in the International Multicenter (1997) trial and in the Noyes et al (1997) study, respectively.

The large US multicentre study on moclobemide in the treatment of Social Anxiety Disorder in 583 patients failed to detect a dose-response curve and consequently a consistent difference between the active drug and placebo (Noyes et al 1997). Methodological problems should be considered when one interprets the results of this study. The placebo response rate was high, 32%, as is usual in large multicentre studies in most psychiatric disorders. Five different levels of fixed doses of moclobemide (75, 150, 300, 600 and 900 mg) were compared to the placebo group making the trial a 6-treatment groups study in 506 patients eligible for the efficacy analysis. The dropout rate was high, 31.2%, reducing the number of patients for the analysis of observed cases to 348 cases. This study of Noyes et al (1997) may have been under-powered for the very ambitious task of detecting a fine-tuned dose response curve between 5 different fixed doses of moclobemide in comparison with placebo.

Brofaromine, another reversible inhibitor of monoamine oxidase (RIMA), has been studied in three double-blind placebo-controlled studies in the treatment of Social Anxiety disorder. In a small study with 30 patients van Vliet et al (1992) employing 150 mg/day of brofaromine detected a marked therapeutic effect of the active drug in comparison with placebo, 73% versus 0.0% responders according to the CGI, respectively. The absence of placebo responders in this study may have been related to a highly selected sample from a single specialised centre. A second study with brofaromine with positive therapeutic results in Social Anxiety Disorder has been carried out by Fahlen et al (1995) in 77 patients also with a 150-mg/day dose with response rates of 78% and 20% in the brofaromine group and in the placebo group, respectively. The third placebo-controlled study with brofaromine in the treatment of Social Anxiety Disorder yielded results discussed by the authors as not so positive relative to efficacy due to a smaller decrease in the total score of the LSAS (Liebowitz Social Anxiety Scale) probably because of a smaller mean daily dose of the drug, 107 mg, relative to the previous studies in which 150 mg/day of brofaromine had been employed (Lott et al 1997).

Benzodiazepines

Clonazepam was studied in the treatment of Social Anxiety Disorder in a double-blind placebo-controlled trial with 75 patients assessed in an initial acute study period of 10 weeks followed by a long-term extension with a mean daily dose of 2.4 mg (range 0.5 to 3 mg). There was a high response rate in the active drug group of 78.3% versus 20.0% in the placebo group according to the CGI scores of 1 or 2 (very much improved and much improved) (Davidson et al 1993). As can be seen in Table 1, the assessments of the patients in this clonazepam study with the LSAS (Liebowitz Social Anxiety Scale) were also associated with a high degree of improvement in the active drug group, with a difference of 31% of clonazepam over placebo in the reduction of the LSAS mean total score. The results from the study by Davidson et al (1993) with a low placebo response rate of 20.0% and a large difference between the therapeutic effects of the drug and placebo are another example of a set of findings that tend to emerge from a single centre specialised in Social Anxiety Disorder.

Bromazepam was investigated in a double-blind placebo-controlled trial in the treatment of 60 cases of Social Anxiety Disorder with a mean

daily dose of 21 mg in a 12-week treatment period (Versiani et al 1997). In this study, bromazepam was statistically significantly superior to placebo in all outcome measures at weeks 8 and 12 of the study period and associated with a high response rate of 82% versus 20.0% in the placebo group. In the LSAS (Liebowitz Social Anxiety Scale) the mean scores decreased markedly in the bromazepam treated patients, with a reduction of 70% in the mean total score at end-point. The difference in this bromazepam study in the reduction of the mean total score of the LSAS between the drug and placebo groups was very marked, 63% (Table 1) (Versiani et al 1997).

Gapapentin and Buspirone

In a double-blind placebo-controlled trial, van Vliet et al (1997) could not confirm earlier findings from open studies suggesting the efficacy of buspirone in the treatment of Social Anxiety Disorder. There were only two responders in their study, one in the buspirone group and one in the placebo group.

Gabapentin in a mean dose of 2.100 mg/day has been compared to placebo in the treatment of Social Anxiety Disorder in 69 cases with the demonstration of moderate efficacy of the drug; 32% of the gabapentin treated patients being responders according to the CGI versus 14% in the placebo treated group (Pande et al 1999).

Serotonin Reuptake Inhibitors (SRIs)

A small study with fluvoxamine in 30 cases of Social Anxiety Disorder at a low fixed daily dose of 150 mg (50 mg t.i.d.) yielded results showing superiority of the drug over placebo with a rate of responders of 46% versus 7.0%, for the drug and the placebo respectively (van Vliet et al 1994). The very low placebo response rate of 7.0% , or one single patient out of 15, in this study, can be partially explained by the criterion of responder employed by van Vliet et al (1994); i.e. a decrease of 50% or more in the LSAS. If the investigators had employed the CGI, the rates of responders would probably have been higher in both treatment groups.

In a larger study with fluvoxamine in 92 patients with Social Anxiety Disorder with a larger and flexible dose (mean = 202; s.d.=86) employing the CGI (Clinical Global Impression of Improvement) scores of 1 or 2 (very much improved or much improved) as the primary efficacy parameter, a higher proportion of responders was found in the fluvoxamine treated patients (42.9%) than in the placebo treated ones (22.7%) (MB Stein et al 1998). The placebo response rate in this study was low as assessed by the CGI or by the reduction in the LSAS total score, which was only 4.0 points (Table 1).

Sertraline has been studied in the treatment of Social Anxiety Disorder in a small sample of 12 patients but with a sophisticated cross-over design, with a mean daily dose of 133 mg/day. The sertraline treated patients improved significantly more as assessed with the LSAS than those treated with placebo. There was a difference of 29% between the reduction in the total score in the active drug group and the reduction in the placebo group (Katzelnick et al 1995) (Table 1).

Paroxetine has been very well studied in two trials published so far in the treatment of Social Anxiety Disorder. In a study with a 12-week treatment period, paroxetine with a mean daily dose of 37 mg yielded a response rate of 55%, significantly superior to the response rate of 24% obtained in the placebo treated patients according to the criterion of reaching a score of 1 or 2 in the CGI (Clinical Global Impressions of Improvement) (MB Stein et al 1998). In this paroxetine study, mean decreases in the LSAS total score were 30.5 and 14.5 points in the active drug group and in the placebo group respectively, associated with a difference of 21.7% highly significantly favouring paroxetine (95% CI, 8.7% - 34.7%) (MB Stein et al 1998).

In another study, paroxetine has been compared to placebo in 290 patients with Social Anxiety Disorder in a 12-week trial, yielding a proportion of 66% of responders in the active treatment versus 32% in the placebo treated group, according to the CGI criterion of very much improved or much improved (scores 1 or 2) (Baldwin DJ et al 1999). In this second study on paroxetine, reductions in the mean total score of the LSAS were also more marked in the drug-treated patients in comparison with the placebo treated group; 16% greater in the paroxetine group, a statistically significant difference ($p<0.001$).

Comment

In Table 1 the main data from the 19 double-blind, placebo-controlled studies in Social Anxiety Disorder (Social Phobia) are presented. With the exception of the Heimberg et al (1998) study, phenelzine relative to efficacy is clearly superior to the other drugs both according to the greater numbers of responders assessed with the CGI (Clinical Global Impressions of Improvement) and by the more marked decreases in the LSAS (Liebowitz Social Anxiety Scale) scores. Despite the greater efficacy, phenelzine or tranylcypromine, two irreversible classical MAOIs, should be considered as third-line treatments for Social Anxiety Disorder, reserved for very severe treatment resistant cases, due to the risk of very dangerous interactions with foodstuffs or with drugs, potentially fatal or leading to irreversible neurological sequelae.

RIMAs (Reversible Inhibitors of Monoamine Oxidase), moclobemide and brofaromine, are

associated with moderate efficacy in comparison with the irreversible MAOIs but are far better tolerated and, by being reversible, are not associated with the risks of the classical compounds. Brofaromine has not been introduced in the market. Moclobemide (not available in the US) does represent an option for the treatment of Social Anxiety Disorder. Two studies with negative therapeutic results (Schneier et al 1998; Noyes et al 1997) have cast doubt on the efficacy of moclobemide in Social Anxiety Disorder but methodological shortcomings limit their implications. In the Versiani et al (1992) study the response rates (CGI = 1 or 2) of 85%, 65% and 15% for the phenelzine, moclobemide and placebo groups respectively, were associated with statistically significant differences between the proportions of responders in the three groups (phenelzine > moclobemide > placebo; $p < 0.001$). This high power of discrimination between the therapeutic effects of two drugs and placebo in a single centre may be due to its specialisation, ease of recruiting typical cases without comorbidity and fewer raters involved.

Two benzodiazepines, clonazepam and bromazepam, have been markedly efficacious in the treatment of Social Anxiety Disorder in two placebo-controlled studies (Davidson et al 1993; Versiani et al 1997). However, problems associated with the clinical use of benzodiazepines, especially with chronic use, make a benzodiazepine a second-line treatment for Social Anxiety Disorder. In the Versiani et al (1997) study with bromazepam, unwanted effects were frequent and marked and discontinuation of the drug was associated with important withdrawal phenomena.

The overall reduction in the LSAS mean total score with the various drugs in different studies tends to be inferior to 50% especially in multicentre trials (Table 1). Social Anxiety Disorder is a long-lasting, chronic condition and it may take more than 12 weeks to achieve greater degrees of improvement.

Noteworthy in this set of controlled studies (Table 1) on the treatment of Social Anxiety Disorder is the consistent trend of low placebo response rates of about 20% in trials carried out in single and/or specialised centres versus larger placebo response rates in multicentre trials. Multicenter studies with large sample sizes are more representative of the "real world" the treatments will encounter in clinical practice. Clinical trials carried out in single specialised centres are more sensitive to differences between drugs and placebo. One might consider the two types of trials as dealing with different objectives.

The efficacy of SRIs in the treatment of Social Anxiety Disorder has been consistently determined in well-designed and well-performed controlled studies. Paroxetine is the SRI best studied in the treatment of Social Anxiety Disorder. Due to better tolerability and fewer problems in long-term treatment in comparison with classical MAOIs or with benzodiazepines, SRIs, particularly Paroxetine, are the first-line treatment for Social Anxiety Disorder at present.

Table 1 - Randomized placebo-controlled double-blind studies in Social Anxiety Disorder (Social Phobia)

Drug	Reference	N	Dose Mean mg/day	Responders % CGI (1-2) or [a] ↓ LSAS > 50%		Liebowitz Social Anxiety Scale (LSAS) Total Score Means				
				Drug	Placebo	Baseline (drug)	Change Drug (-)	Change Placebo (-)	Difference Drug/ Placebo %	Decrease Drug %
Phenelzine	Gelernter et al. 1991	65	55	69	20	-	-	-	-	-
Phenelzine	Liebowitz et al., 1992	74	76	64	25	75.2	34.1	6.9	36	45
Phenelzine	Versiani et al., 1992	78	68	85	15	68.5	54.5	9.0	66	79
Phenelzine	Heimberg et al., 1998	133	60	52	30	67.3	35.4	24.2	17	53
Atenolol	Liebowitz et al, 1992	74	98	30	25	67.4	10.4	6.9	5	15
Moclobemide	Versiani et al., 1992	78	580	65	15	63.3	36.3	9.0	43	57
Moclobemide *	International, 1997	578	Placebo3		34	81.3		19.9		
			00	41		79.3	25.8		10	33
			600	47		80.2	29.3		12	37
Moclobemide	Schneier et al., 1998	77	728	18	13	75.2	12.6	4.5	11	17
Moclobemide	Noyes et al., 1997	583	placebo	32	n.a.	n.a.	n.a.	n.a.	n.a.	
			75	28						
			150	41						
			300	40						
			600	35						
			900	37						
Brofaromine	van Vliet et al., 1992	30	150	73	0	71.2	34.2	9.1	35	48
Brofaromine	Fahlen et al., 1995	77	150	78	20	67.2	32.8	12.0	31	49
Brofaromine	Lott et al., 1997	102	107	50	19	81.8	19.2	9.1	13	24
Clonazepam	Davidson et al., 1993	75	2.4	78	20	78.3	40.2	15.8	31	51
Bromazepam	Versiani et al., 1997	60	21	82	20	88.8	62.2	5.6	63	70
Fluvoxamine *	van Vliet et al., 1994	30	150	46 a	7 a	68.1	30.4	11.1	29	45
Fluvoxamine	MB Stein et al., 1998	92	202	43	23	81.0	23.0	4.0	24	29
Sertraline	Katzelnick et al., 1995	12	133	n.a.	n.a.	65.5	26.8	7.8	29	41
Paroxetine	MB Stein et al., 1998	187	37	55	24	78.0	30.5	14.6	21	39
Paroxetine	Baldwin et al, 1999	290	35	66	32	87.6	29.4	15.6	16	37
Buspirone *	van Vliet et al., 1997	30	30	3 a	3 a	n.a.	n.a.	n.a.	n.a.	n.a.
Gabapentin	Pande et al., 1999	69	2.100	32	14	87.4	27.3	11.9	17	31

N.A. Not available in the reference; (*) fixed doses; (-) diminishment; CGI Clinical Global Improvement; ([a])↓, total LSAS > 50%

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The Genetic Heterogeneity of "Schizophrenia"

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Summary

The main reason for the inconsistent findings in schizophrenia research is the lack of diagnostic conformity. This has not changed markedly following the introduction of modern operational diagnostic systems. Taking schizophrenia as a disease entity or assuming schizophrenic spectrum psychoses to represent a continuum of diseases without any clear dividing lines, the results of family and twin studies point to a multifactorial etiology based on a polygenic mode of transmission. Further, then it has to be assumed a familial continuum from schizophrenia to affective psychosis and other spectrum disorders. However, in family and twin studies based on Leonhard's classification, there is clearcut evidence that schizophrenic spectrum psychoses have to be divided into clinical and etiological subgroups with a completely different genetic background. For example, systematic catatonia is, for the most part, a sporadic disease, whereas periodic catatonia aggregates in families in a manner consistent with a major gene effect. Further, the results indicate that schizophrenic spectrum psychoses consist of three main valid categories: cycloid psychoses, unsystematic schizophrenias and systematic schizophrenias. In the case of cycloid psychosis and systematic schizophrenias, genetic loading seem to be very low, while "environmental" factors, for example, birth complications, may play an important etiological role. Unsystematic schizophrenias, however, are predominantly inherited and "environmental" factors are not very prominent.

Key words: *schizophrenia, genetic heterogeneity, twin studies, family studies.*

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Introduction

From the beginning, the diagnostic concept of schizophrenia has been a matter of dispute and one main reason for the inconsistent findings in schizophrenia research is the lack of diagnostic conformity. In modern literature, conflicting results in schizophrenia research are mostly thought to be an indication of polygenic and heterogenic inheritance combined with various adverse environmental factors. However, up to now it remains an open question whether schizophrenia and schizophrenia-like psychoses represent a continuum of diseases without clear dividing lines or whether there are distinct disease entities with various different etiologies.

Family and twin studies based on schizophrenia as one disease entity

Based on the Kraepelinian concept of chronically dissociative and avolitional processes in schizophrenia, early European family studies found a risk of 6.6 - 8.1 % morbidity in first-degree relatives of schizophrenics (Gottesman and Schields 1982; Slater and Cowie 1971). Making an extraordinarily narrow definition of schizophrenia, others found no evidence of familial transmission (Abrams and Taylor 1983; Pope et al 1982). Most recent family studies have used structured psychiatric assessment and operational diagnostic criteria (APA 1987). In some of these studies familial aggregation of schizophrenia was not convincing (Coryell and Zimmerman 1988; Gershon et al 1989), but others found a 10 times elevated risk of relatives of schizophrenics compared to controls. Kendler et al (1993) and Maier et al (1993) reported a cumulative risk in first-degree relatives of 6.5% and 5.2%, respectively.

Homogeneity of familial morbidity was often observed (Gottesman and Shields 1982; Scharfetter and Nüsperli 1980). Differentiating schizophrenia into the clinically subtypes of hebephrenic, catatonic and paranoid syndromes, Kallmann (1938) found in the catatonic type a high familial incidence of homogenous psychoses amounting to 18.8% in parent-child pairs and a significantly increased morbidity risk of 9.6% in sibs. Weinberg and Lobstein (1943), Hallgren and Sjogren (1959), and Scharfetter and Nüsperli (1980) reported significantly increased morbidity risk in first-degree relatives of catatonic patients compared to patients with paranoid and hebephrenic-type

schizophrenia. However, using gross diagnostic categories or factor analysis of symptoms, others again questioned familial homogeneity of psychopathology (Kendler et al 1988; Leboyer et al 1992). The results of these studies were interpreted as being consistent with a familial continuum from schizophrenia to affective psychosis and spectrum disorders (Crow 1986, Maier et al 1993).

Another approach for revealing genetic contribution to psychiatric diseases is the twin research strategy. The classical twin method deals with studies of twin concordance, i.e. comparison of monozygotic and dizygotic pairs with respect to concordance rates, and studies of twin discordance, i.e. comparison of the ill index-twin with the healthy co-twin with respect to selected variables. A disease is thought to be genetically determined if the concordance rate of monozygotic pairs is significantly higher than that of dizygotic pairs. Mainly "environmental" causation has to be assumed if there is no substantial difference between monozygotic and dizygotic concordance rates.
All the most important twin studies in schizophrenia found significantly higher concordance rates in monozygotic twins compared to dizygotic twins pointing to a major genetic component in its etiology. However, the rate of concordance substantially varied between the studies (Propping 1989). Obviously, the different studies have been dominated by various patient groups which have either raised or lowered the concordance rates. Some authors have reported significantly different concordance rates with regard to the severity of illness in the index-twins. Index-twins suffering from mild or transient schizophrenia have been found to have ill co-twins in only 17-33% of cases, whereas pairs with index-twins exhibiting severe residual psychopathology have had concordance rates of 75-100% (Gottesman and Shields 1966, 1982; Inouye 1961; Kallmann 1946). These findings are generally interpreted that a quantitatively higher genetic loading in individuals with severe residual psychopathology is causal for the higher concordance rates compared to individuals with a quantitatively lower genetic loading (Kringlen 1960). The possibility of a qualitatively different genetic background or of a completely different etiological background only scarcely was taken into consideration.
As a consequence, nowadays most authors suggest that schizophrenia is a disease spectrum with a multifactorial etiology based on a polygenic mode of transmission (Kidd 1981; Tsuang et al 1991).

Family and twin studies based on Leonhard's nosology

The Wernicke-Kleist-Leonhard school postulated various and etiologically distinct endogenous psychoses with different patterns of heredity (Leonhard 1999; Ungvari 1993). Thorough follow-up investigations lead to a classification of the endogenous psychoses into 5 main categories according to different symptomatology, long-term course, and outcome:
1. Unipolar phasic psychoses
2. Bipolar phasic psychoses
3. Cycloid psychoses
4. Unsystematic schizophrenias
5. Systematic schizophrenias

There is growing evidence that this classification is of outstanding reliability and validity (Astrup 1979; Ban 1990; Beckmann et al 1990; Fish 1964; Franzek and Beckmann 1992; Franzek and Beckmann 1998; Stöber et al 1995; Strik et al 1993; Ungvari 1985; Warkentin et al 1992).
Based on highly operationalized and sophisticated clinical descriptions and hierarchical symptom patterns, the psychoses exhibiting so-called "schizophrenic" symptoms have to be divided into three nosological subgroups: cycloid psychoses, unsystematic and systematic schizophrenias. Cycloid psychoses run a phasic and prognostically favourable long-term course which is similar to manic-depressive disease. Complete remissions of every acute psychotic episode and absence of residual psychopathological symptoms in the long run are characteristic features of cycloid psychoses. In the early beginning there may be some resemblance between cycloid psychoses and unsystematic schizophrenias, however, in the long run unsystematic schizophrenias lead to residual states of varying severity and there are no major difficulties to distinguish them from cycloid psychoses. Systematic schizophrenias usually begin insidiously and run a chronic, progressive course without remission. Their irreversible, treatment-resistant residual states (Beckmann et al 1992) are clinically well defined and can be reliably distinguished from unsystematic schizophrenia. Leonhard draws a sharp nosological line between cycloid psychoses, systematic and unsystematic schizophrenias. In the following the results of family and twin studies based on this nosological approach are presented.

Family study on catatonic schizophrenia differentiating in systematic and periodic catatonia

The study was designed to test whether the clinical different groups of systematic and periodic catatonias emanate from different genetic backgrounds (Beckmann et al 1996). Probands were chosen from inpatients and outpatients at the Department of Psychiatry, Wurzburg University, and from wards with chronically ill patients at the Lohr/Main State Hospital. The patients group consisted of 83 patients (41 women, 42 men) with periodic catatonia and 56 patients (14 women, 42 men)

with systematic catatonia. All Patients fulfilled diagnostic criteria for schizophrenia according to DSM-III-R.
Systematic catatonic patients (n=56) had 223 first-degree relatives, 112 parents and 111 siblings. There were 3 unknown fathers.
Periodic catatonic patients (n=83) had 328 first-degree relatives, 166 parents and 162 siblings. There were 5 unknown fathers.
Using the conservative approach of live-table analysis based on Kaplan-Meyer method, the morbidity risks were separately calculated for mothers, fathers and sibs. The difference in life-table curves for the two different diagnostic groups was determined by the log-rank x^2 statistics with one degree of freedom. Unknown fathers were excluded from analysis. Thus, the study based on 109 parents and 111 siblings of systematic catatonic patients and 161 parents and 162 siblings of periodic catatonic patients.

Thirty-three of the 161 parents (20.5%) and 26 of the 162 siblings (16.0%) of periodic catatonic probands were afflicted with schizophrenia according to the case notes. Thirty-two of the 59 afflicted relatives (76%) could be personally examined. All of them presented residual states characteristic of periodic catatonia. In contrast, only four of the 109 parents (3.7%) and 3 of the 111 siblings (2.7%) of systematic catatonic probands were afflicted with schizophrenic psychoses *(Table 1)*.
Figures 1,2, and 3 show the morbidity risks of fathers, mothers and siblings in comparison of systematic and periodic catatonic probands according to the life-table analysis based on Kaplan-Meyer method. The morbidity risk of first-degree relatives of peridiodic catatonic probands was significantly higher than that of first-degree relatives of systematic catatonic probands.
In 8 out of the 83 families (10%) of periodic catatonic probands 3 or more successive generations of family members had suffered from catatonic psychoses and received hospital treatment. Figure 4 presents one example of them.

Table 1
Percentage of schizophrenic first-degree relatives in comparison of systematic and periodic catatonic probands (modified according to Stöber et al 1995)

First-degree relatives	Systematic catatonia	Periodic catatonia
Fathers	1.9%	14.1%
Mothers	5.4%	26.5%
Brothers	4.9%	15.9%
Sisters	0 %	16.3%
All	**3.2%**	**18.3%**

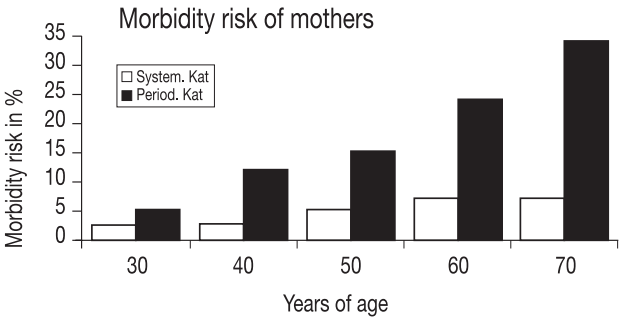

Figure 1
The life-table analyses of the mothers' morbidity risk of schizophrenia revealed statistically highly significant differences between mothers of periodic catatonic and mothers of systematic catatonic probands ($p < .005$). There was an increase in the risk for mothers of systematically catatonic patients up to about 7%. In mothers of periodic catatonic probands, however, the morbidity risk rises up to about 34%.

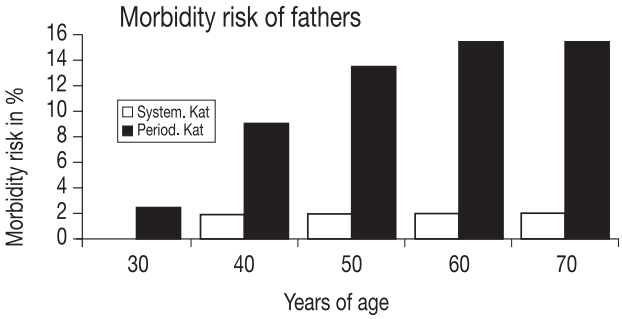

Figure 2
The life-table analyses of the fathers' morbidity risk of schizophrenia revealed statistically significant differences between fathers of periodic catatonic and fathers of systematic catatonic probands ($p < .05$). There was an increase in the risk for fathers of systematically catatonic patients up to about 2%. In fathers of periodic catatonic probands, however, the morbidity risk rises up to about 16%.

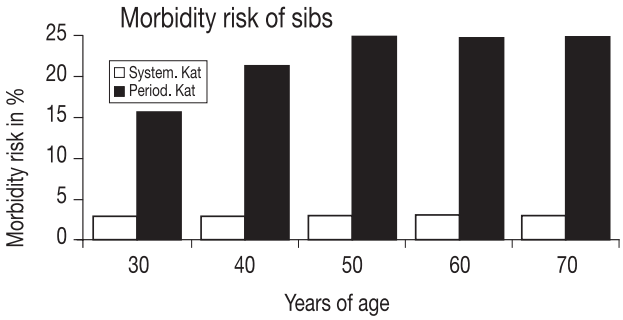

Figure 3
The life-table analyses of the siblings' morbidity risk of schizophrenia revealed statistically highly significant differences between siblings of periodic catatonic and siblings of systematic catatonic probands ($p < .01$). There was an increase in the risk for siblings of systematically catatonic patients up to about 3%. In siblings of periodic catatonic probands, however, the morbidity risk rises up to about 25%.

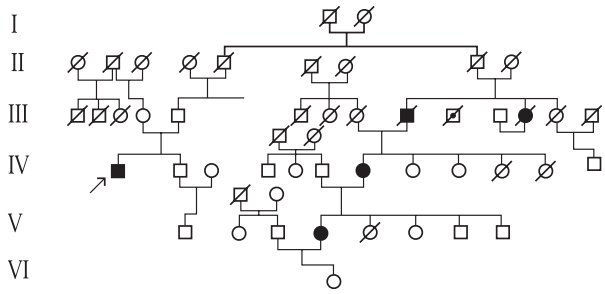

Figure 4
Familial aggregation of periodic catatonia in an extended pedigree. Circles represent women, squares men, slashed symbols deceased individuals, target symbols suicides, solid symbols individuals who received hospital treatment for periodic catatonia, the arrow indicates the proband.

Thirty-one probands of periodic catatonic patients had a total of 33 ill parents. In 2 patients both parents were afflicted. Nine probands had ill fathers and 20 probands ill mothers. In these 29 cases of unilineal paternal transmission the phenomenon of anticipation occurred, i.e. probands had a significantly earlier age of onset compared to their parents. Further, there was no linear relationship between age at initial hospitalisation in probands and their parents, i.e. anticipation was also clearly obvious in probands with early-onset parents. This indicates that true anticipation occurred (Stöber et al 1995).
In summary, these findings provide clearcut evidence that systematic catatonia, for the most part, is a sporadic disease, whereas periodic catatonia aggregates in families in a manner consistent with a major gene effect.

Twin study on schizophrenic spectrum psychoses differentiated in cycloid psychoses, unsystematic and systematic schizophrenias

In order to examine the specificity and validity of diagnoses, Franzek and Beckmann (1998) carried out a twin study with index-twins suffering from schizophrenic spectrum psychoses. Using different diagnostic systems (DSM-III-R, Leonhard classification), the authors examined twin concordance, family history and the frequency and severity of birth complications of 22 monozygotic and 23 dizygotic twin pairs.
All twin individuals in the Region of Lower Franconia born after 1930 and hospitalised for psychiatric disease were ascertained. Lower Franconia is a region of Bavaria, the population of which is characterised by low fluctuation owing to new arrivals and emigration. First, all twins with ICD 9 diagnoses of schizophrenic psychoses (295.0 - 295.9) and paranoid syndromes (297.0 - 297.9) were selected. To enter the study, the index-twins then had to fulfil the diagnostic criteria of the following categories of DSM-III-R: Schizophrenia (295.1, 295.2, 295.3, 295.6, 295.9), psychotic disorders not otherwise classified (295.30, 295.40, 295.70, 298.80, 298.90) and delusional (paranoid) disorders (297.10). These DSM-III-R categories comprised by definition "psychoses of the schizophrenic spectrum". The zygosity diagnoses were based on molecular genetic methodology (Erdmann et al 1993) and the zygosity questionnaire according to Torgersen (1979) was also used. Since the diagnosticians were not aware of twin zygosity, only same-sex twin pairs entered the study. It was also thought that this strategy would exclude obvious differences in treatment attributable to the difference in sex (for example, minting as a female or male). All twins were personally examined by two psychiatrists (H.B. and E.F.), working independently and formulating diagnoses according to the criteria of DSM-III-R and Leonhard's nosology. E.F. diagnosed one of the twin partners and not until E.F. had formulated his diagnosis was the twin's partner presented to H.B. H.B. received no information on E.F.'s diagnosis until he had committed himself to a specific diagnosis within DSM-III-R and Leonhard's classification. He received all the relevant information except for the family history, the history of the mothers' pregnancies and deliveries, and except for the mental state of the twin's partner. This methodological approach was thought to minimise the likelihood of the diagnosis of one twin influencing the diagnosis of his/her partner, as would have been possible if both partners of a given twin pair had been diagnosed by the same investigator.

According to Gottesman and Shields (1982) concordance criteria were gradated into 3 groups: strict, middle and broad. Strict concordance means that the co-twin's diagnosis was identical to that of the index-twin. Middle concordance means that the co-twin's diagnosis was not identical to that of the index-twin but belonged to the schizophrenic spectrum, and broad concordance means that the co-twin was not psychotic but suffered from another psychiatrically relevant mental disorder, i.e. alcohol abuse, personality disorder etc. Concordance was determined using pairwise and probandwise calculation method. Probandwise concordance implies that pairs with two index-twins have to be counted twice. This method of calculation presupposes that the index-twins were ascertained systematically as it was done in the study and allows a direct comparison of concordance rates with the values for familial loading in family studies (McGue 1992).

Table 2 shows pairwise and table 3 probandwise concordance rates of the study. The middle concordance criteria are the best for direct comparison with the most important twin studies in the literature.

Table 2
Pairwise concordance (age-corrected values in parentheses)

Diagnoses of index-twins	Concordance criteria	MZ pairs	DZ pairs
Psychoses of the schizophrenic spectrum (22 MZ, 23 DZ)	strict	46% (50%)	17% (24%)
	middle	50% (55%)	22% (31%)
	broad	64% (70%)	26% (37%)
Schizophrenia according to DSM-III-R (9 MZ, 12 DZ)	strict	67% (67%)	17% (18%)
	middle	78% (78%)	25% (27%)
	broad	100%	25% (27%)
295.4, 295.7, 297, 298 according to DSM-III-R (13 MZ, 11 DZ)	strict	31% (36%)	18% (21%)
	middle	31% (36%)	18% (21%)
	broad	39% (45%)	27% (32%)
Systematic schizophrenias according to Leonhard (0 MZ, 6 DZ)	strict		0%
	middle		0%
	broad		0%
Unsystematic schizophrenias according to Leonhard (11 MZ, 8 DZ)	strict	82% (82%)	38% (40%)
	middle	82% (82%)	38% (40%)
	broad	100%	50% (53%)
Cycloid psychoses according to Leonhard (11 MZ, 9 DZ)	strict	27% (33%)	22% (26%)
	middle	27% (33%)	22% (26%)
	broad	27% (33%)	22% (26%)

The pairwise concordance of a metaanalysis of twin studies between 1928 and 1991 was 55% in monozygotic pairs and 11% in dizygotic pairs. Using the middle concordance criteria, monozygotic concordance was only slightly lower (50%) in the total sample of the study, i.e. in the schizophrenic spectrum psychoses. The probandwise concordance of the metaanalysis was 58% in monozygotic pairs and 15% in dizygotic pairs. Using the middle concordance criteria, monozygotic concordance was only slightly higher (65%) in the total sample of the study.

The highest concordance rates for monozygotic twins were obtained in the diagnostic group of unsystematic schizophrenias according to Leonhard. Monozygotic twins fulfilling the strict criteria of DSM-III-R schizophrenia also revealed very high concordance rates. The broad definition of concordance led to an increase of up to 100% for both unsystematic schizophrenia and DSM-III-R schizophrenia. With regard to the dizygotic pairs, a broadening of the definition of concordance did not change the concordance rate for DSM-III-R schizophrenia (25%), but did cause the rate for unsystematic schizophrenia to increase from 38% to 50%. Inherited characteristics that are noticeable to 100% in monozygotic twins are expected to be apparent in 50% of dizygotic twins. A fall in dizygotic concordance below 50% can be explained only by factors associated with the different social environment of monozygotic and dizygotic twins. In this study, the difference in dizygotic concordance rates between unsystematic schizophrenia and DSM-III-R schizophrenia is caused by the fact that the 6 dizygotic discordant pairs with systematic schizophrenic index-twins had to be allocated to the DSM-III-R schizophrenic group.

Table 3
Probandwise concordance (age-corrected values in parentheses)

Diagnoses of index-twins	Concordance criteria	MZ twins	DZ twins
Psychoses of the schizophrenic spectrum (31 MZ, 25 DZ)	strict	61% (65%)	24% (33%)
	middle	65% (69%)	28% (38%)
	broad	74% (79%)	32% (44%)
Schizophrenia according to DSM-III-R (14 MZ, 12 DZ)	strict	79% (79%)	17% (18%)
	middle	86% (86%)	25% (27%)
	broad	100%	25% (27%)
295.4, 295.7, 297, 298, according to DSM-III-R (17 MZ, 13 DZ)	strict	47% (53%)	31% (35%)
	middle	47% (53%)	31% (35%)
	broad	53% (60%)	39% (44%)
Systematic schizophrenias according to Leonhard (0 MZ, 6 DZ)	strict		0%
	middle		0%
	broad		0%
Unsystematic schizophrenias according to Leonhard (18 MZ, 8 DZ)	strict	89% (89%)	38% (40%)
	middle	89% (89%)	38% (40%)
	broad	100%	50% (53%)
Cycloid psychoses according to Leonhard (13 MZ, 11 DZ)	strict	39% (45%)	36% (41%)
	middle	39% (45%)	36% (41%)
	broad	39% (45%)	36% (41%)

The concordance rates for monozygotic pairs in the group of DSM-III-R categories 295.4, 295.7, 297 and 298 and in the diagnostic group of cycloid psychoses were substantially lower. In the group of cycloid psychoses, in particular, the monozygotic concordance rate did not differ from the dizygotic rate. A broadening of the definition of concordance did not change these rates. This is indicative that in cycloid psychoses there is almost no genetic component in their etiology.

It is striking that there were no MZ twins with a diagnosis of systematic schizophrenia. On the other hand, 6 out of 25 (24%) psychotic dizygotic index-twins suffered from systematic schizophrenia. This difference is statistically highly significant.
Leonhard has investigated 69 psychotic monozygotic twins and also did not find systematic schizophrenia, while this was the case in 12 out of his 47 (25.5%) psychotic dizygotic twins.

Leonhard assumed that the close contact that is usually present in monozygotic twins may prevent the disease and that conversely, a lack of communication during certain developmental stages of childhood may be one of the psychosocial etiological factors of systematic schizophrenia. Ever since Spitz (1945), it has been well known that a lack of the appropriate emotional care in early childhood can cause severe mental disturbance.

As Leonhard did not carry out a systematic twin ascertainment, he may have overlooked monozygotic twins with systematic schizophrenia. However, despite a systematic twin ascertainment in this study, there were no monozygotic twins with systematic schizophrenia. This clearly defeats the theory that "confusion of ego identity" is one causal factor for systematic schizophrenia, as it has been proposed by some authors (Jackson 1959).

Table 4 presents the family history data of the 45 twin pairs with regard to diagnostic distribution. Familial loading has been differentiated between loading with schizophrenia, affective psychosis, and suicide without prior psychiatric diagnosis and/or non-psychotic but other mental disturbances (such as alcohol abuse, personality disorder, chronic insomnia etc.).

Table 4
Familial loading (parents and siblings) with mental disorders of the 45 twin pairs with regard to diagnoses of the index-twins

Diagnoses of index-twins	Schizophrenia	Affective psychosis	Suicide and/or other psychiatric diagnosis except for psychosis
Schizophrenia (DSM-III-R) (70 parents and siblings)	8.6 %	2.9 %	20.0 %
295.4, 295.7, 297, 298 according to DSM-III-R (117 parents and siblings)	1.7 %	6.8 %	12.8 %
Unsystematic schizophrenia according to Leonhard (65 parents and siblings)	12.3 %	4.6 %	33.8 %
Systematic schizophrenia according to Leonhard (22 parents and siblings)			13.6 %
Cycloid psychoses according to Leonhard (100 parents and siblings)		7.0 %	4.0 %

There were more schizophrenic and fewer affective psychotic parents and siblings in the group of DSM-III-R schizophrenia than in the group comprising DSM-III-R categories 295.4, 295.7, 297, 298. This difference was not statistically significant, however. On the other hand, statistically significant results emerged when the diagnostic groups cycloid psychoses and unsystematic schizophrenias were compared. Unsystematic schizophrenic twins had significantly more schizophrenic and otherwise mentally disturbed parents and siblings than cycloid psychotic twins ($p < .05$, contingency test, df=3, $x^2=9.205$) and there was neither a schizophrenic parent nor a schizophrenic sibling in the families of cycloid psychotic twins.

It is noticeable that 7% of the 100 parents and siblings of cycloid psychotic twins suffered from affective psychoses (84% of the cycloid psychotic twins had been allocated to the diagnostic group comprising DSM-III-R categories 295.4, 295.7, 297, 298, which explains the finding that in this diagnostic heterogenous group a great proportion of first-degree relatives with affective psychoses have also been found). This may indicate that cycloid psychoses have to be drawn near the proximity of affective psychoses. The assumption, however, that cycloid psychoses are merely a variant of manic-depressive disorder is not tenable, since manic-depressive disorder exhibits high monozygotic and low dizygotic discordance rates (Bertelsen et al 1977) which indicates high genetic loading and which is at clear variance with our findings for cycloid psychoses.

In the group of monozygotic cycloid psychotic twins the frequency and severity of birth complications for the ill or more severely affected twins was higher to a statistically significant degree than for their partners ($p < .05$). The dizygotic index-twins suffering from systematic schizophrenia according to Leonhard ($n = 6$) had complications which were three times more frequent and more severe than in their healthy co-twins. There was no difference between the ill or more severely affected twins and their partners in the diagnostic groups of DSM-III-R schizophrenia and unsystematic schizophrenia.

Thus, the findings of this twin study provide strong evidence that schizophrenia and quasi-schizophrenic psychoses comprise a spectrum of genetically heterogenous diseases. This was much more striking in Leonhard's nosology compared to DSM-III-R diagnostic criteria. Cycloid psychoses, unsystematic and systematic schizophrenias seem to be valid and etiologically different subgroups of the schizophrenic spectrum.

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VIEWPOINT ▸

Reappraisal of Dementia Praecox: Focus on Clinical Psychopathology

Carlos Roberto Hojaij

Summary
One century of investigation in schizophrenia is still not enough to elucidate all the complex issues related to the essential symptomatology, clinical boundaries, aetiology, pathogenesis, outcome, treatment and prevention. Despite the extraordinary progress in the neuroscience field, no definitive data is available for schizophrenia. On the other hand, after the successful activity of the psychopharmacological era, the clinical psychopathological investigations were reduced and almost replaced by the mechanistic operational diagnosis. This has caused an impoverishment in psychiatry. Tracing some historical aspects of schizophrenia since the kraepelinian Dementia Praecox, this article intends to demonstrate the failure of the current model of diagnosis and current limitation of neuroscience. It advocates the reinforcement of Clinical Psychopathology as the foundation for correct and appropriate first steps in the investigation of schizophrenia. The splitting disease is still a challenge to biological psychiatry.

Key words: *schizophrenia, psychopathology, methodology, psychosis, endogenous psychosis.*

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"Dementia Praecox consists of series of states, the common characteristic of which is a peculiar destruction of the internal connections of the psychic life."
"I consider it an open question whether the same morbid process is not after all the cause of the divergent forms, though differing in the point of attack and taking a varying course."
Emil Kraepelin (in "Dementia Praecox', 1886)

Introduction

Schizophrenia is still the very big challenge for biological psychiatry because, after one century of modern investigation into schizophrenia, psychiatrists are not able to accurately certify its cause(s), properly identify the pathophysiological process, circumscribe clearly its clinical pictures, precisely distinguish its boundaries from other psychopathological syndromes, successfully provide efficient and definite treatment, and are not able to instruct on its prevention.

Despite the extraordinary progress in the field of neuroscience, the deep dedication and fruitful knowledge coming from the lab researchers, psychiatry is still in debt to schizophrenia. Psychiatry - and the modern biological psychiatry - still needs the knowledge brought by the clinical approach. Guided by the clinical approach, the psychiatrist maintains the humanistic posture in front of the patient, makes use of empathy, exercises the medical-patient relationship (that still exists), and provides, if not the best treatment, the necessary comfort to the one who is suffering from this splitting disease.

This article intends to celebrate 100 years of the most important milestones in the history of psychiatric nosology, under a clinical perspective. In just a few pages, it reviews some aspects (leaving aside many others) of the hundred-year history of Dementia Praecox, and discusses and explores some diagnostic, treatment and research dilemmas. Besides revising the origins of schizophrenia, it should be considered how much psychiatry has evolved in this subject, where it stands and where it is heading. It is valid to ask how much more is known now than at the time of Kraepelin. Are current schizophrenic patients comparatively better and more precisely diagnosed than those of 100 years ago? Has psychiatry been able to really draw the boundaries of Dementia Praecox, or schizophrenia, as a nosological entity? Or is a syndrome with heterogeneous causes acting upon the same cerebral mechanisms? One way or another it remains as an ideal nosological entity (Jaspers' concept 1997) or its diagnosis is done only by exclusion (Schneider's criterion 1959)? Should the term itself, schizophrenia, which intends to reveal all the dramatics of the ruptures of the schizophrenic, be maintained? If so, why not value the extravagant

symptomatology and correlated phenomena of split personality that gave origin to naming the illness schizophrenia? Why does the investigation of schizophrenia not advance in the sharp detail of the psychopathological examination and description, and prefer the adoption of a sterilising semiological pragmatism? Does the elementary division and value of all the enormous symptomatological wealth of schizophrenia in groups of positive-negative and disorganised symptoms (Andreasen & Olsen 1982; Andreasen 1983, 1984) really take into consideration the true semiology of this psychosis (Mojtabai 1999)?

Attempts at definition

The history of psychiatrists who have described and theorised about schizophrenia parallels the history of psychiatry itself. Kraepelin was the first to develop a comprehensive definition of schizophrenia that gained widespread acceptance. In 1886 he used the term Dementia Praecox (taken from Morel) to identify a syndrome that tended to begin early in life (praecox) and produced a pervasive and persistent impairment in many different aspects of the psychic life, "a more or less well-marked mental enfeeblement (dementia): Dementia Praecox consists of a series of states, the common characteristic of which is a peculiar destruction of the internal connections of the psychic personality" (Kraepelin 1919).

Among the symptoms that compose the whole picture of Dementia Praecox, one may find: unsteadiness of attention, hearing of voices giving commands, influences on thought, constraint of thought, morbid tactile sensations, morbid sexual sensations, loss of mental activity, derailments in linguistic expression, neologism, stereotypes of all sorts, evasions, delusions, ideas of reference, exalted ideas, emotional dullness, "no human feelings", sudden oscillations of emotional equilibrium, loss of sympathy, sudden outburst of laughter, less sensitivity to bodily discomfort, weakening of volitional impulses, automatic obedience, all sort of catatonic symptoms, autism, scission in personality (Kraepelin 1919). While acknowledging that 13% of his patients had significant remissions for some period of time, Kraepelin found a chronic course and a poor outcome to be important features of the illness: "According to my former grouping into hebephrenic, catatonic and paranoid forms, I had come to the conclusion that in about 8 per cent of the first group and in about 13 per cent of the second group, recovery appeared to take place, while paranoid forms probably never issue in complete recovery" (Kraepelin 1919). In this respect it is important to mention that Kraepelin made a distinction between its "Dementia Praecox" and "other forms of dementia such as are known ... as a result of paralysis, senility or epilepsy." At that point he was not talking about dementia as a result of a pathological process, but just about the appearance of the clinical picture.

"Dementia Praecox" 1886 is a very large work comprising many issues in a methodological presentation, from psychic symptoms, body signs and symptoms (including pupillary disorders, tendon reflexes, vasomotor disorders, blood pressure, respiration, secretion of saliva, temperature, menses, metabolism, nourishment, weight, etc.), clinical forms, course and remissions, to causes, anatomy, differential diagnosis and treatment. At some point Kraepelin tried to establish a relationship between the "morbid anatomy and the clinical picture: ... the disease attacks by preference the frontal areas of the brain, the central convolutions and the temporal lobes..." (Kraepelin 1919). In a comparative study of Dementia Praecox involving 100 Javanese patients plus 25 Chinese patients and 100 European patients, Kraepelin (also a pioneer in cultural psychiatry) reached conclusions concerning the universality of schizophrenia and the importance of culture as a pathoplastic factor (Dalgalarrondo 1996).
According to Minkowiski (1966), it is possible to conclude from Kraepelin's Dementia Praecox:

1. the inter-changeable characteristic of the symptoms
2. the principle of hereditary similarity
3. the specificity of terminal states
4. the confrontations with the manic-depressive psychosis.

Bleuler followed Kraepelin with further descriptions and in 1911 recommended that the group of schizophrenias supersede the term Dementia Praecox. It is worthwhile quoting from Bleuler's definition of schizophrenia: "We designate 'dementia praecox' or 'schizophrenia' a group of psychosis determined by an evolution sometimes chronic, sometimes defined by intermittent attacks, that can be interrupted or retrocede at any time, but that do not permit a complete *restitutio ad integrum.* (...) we are facing more or less a clear breakdown of the psychic functions. If the disease is severe, there is a loss in the personality unity; in different moments different psychic complexes seem to represent the previous personality. The integration of the different complexes and impulses is not enough, or even does not exist. (...) It is not possible to demonstrate primary disturbances in perception, orientation and memory. In serious cases it seems to be a complete lack of emotion and affective expressions" (Bleuler 1950). His meticulous descriptions gave rise to the famous "four As" that characterise schizophrenia: association (disturbances), affect (disturbances), ambivalence, and autism. Bleuler (1960) also distinguished the symptomatology of in-

patients from that of outpatients: "in most of the inpatients ... hallucinations, delusional ideas, confusion, stupor, mania, melancholic fluctuations and catatonic symptoms" (accessory symptoms). (...) Outside the hospital there are schizophrenic patients in whom the accessory symptoms are less evident or even do not exist".

Like Bleuler, Schneider (1959) attempted to identify fundamental symptoms that might be helpful in making a psychopathological diagnosis of schizophrenia. In some way different from Kraepelin's importance given to the course of the illness, Schneider (1959) states: "For me, the psychiatric diagnosis is fundamentally based on the clinical pictures, and not on the course". Schneider was influenced by the work of Jaspers (1997) that introduced the Phenomenology and the Comprehensive Psychology in Psychiatry, and the important notions of "understanding" and "non-understanding" to the psychopathological phenomena. Schneider concluded that one critical component of schizophrenia was the inability to find the boundaries between self and non-self and a loss of the sense of personal autonomy. This conclusion led him to discuss "first-rank symptoms", which he identified as audible thoughts; voices arguing, discussing, commenting; somatic experiences of passiveness; thought withdrawal; thought broadcasting; delusional perceptions. He also identified second-rank symptoms, such as other disorders of perception, depressive and euphoric mood, and feelings of emotional impoverishment (Schneider 1959). An unrecognised aspect of the schneiderian first-rank symptoms should be emphasised: they are very much based on the Jaspers (1997) studies of disturbances of self-consciousness (activity of the self, unity of the self, identity of the self and awareness of self as distinct from the outside world) and Jaspers' (1997) distinction between primary (non-understandable) and secondary (understandable) delusions.

Schneider's ideas became the conceptual framework for diagnostic classifications. Schneiderian symptoms were incorporated into several standard diagnostic instruments, such as the Schedule for Affective Disorders and Schizophrenia (Endicott & Spitzer 1978), Research Diagnostic Criteria (Feighner et al 1972), Diagnostic and Statistical Manuals (American Psychiatric Association) and the International Classification of Mental Disorders (World Health Organisation). Unfortunately the utilisation of Schneider criteria was not followed by some very important lessons given by this author: first, sometimes - in the absence of at least visible first-rank symptoms - the diagnosis is based on the second-rank symptoms considering the connections of the whole clinical picture; second, in exceptional situations the diagnosis may be based just in behavioural features (physiognomy and mimic); third, sometimes the presence of first-rank symptoms does not necessarily mean this is schizophrenia, since these symptoms could also be present in symptomatic psychosis; and fourth, the psychopathological diagnosis is made by an assemblance of significant symptoms (the total clinical picture), not by a schematic addition of symptoms.

In the line of a clinical (existential) approach, Binswanger (1972) offers a profound vision of the schizophrenic way of being, the eccentricity, an important clue for the apprehension of schizophrenia. A patient of Bumke (cited in his *"Text Book of Mental Diseases"*, 7th edition, 1948) serves as an example: a father places a coffin near a Christmas tree as a gift for his cancerous daughter. In this case of eccentricity the father is missing the capability that would give him condition to-see-abroad and then consider not only what he was offering to his daughter, but also consider his daughter in her circumstance. The father gave a logical destination to the coffin (for what a coffin should be used), not considering, however, the others situation. His reference is solely the gift (a useful gift) to a person in agony who will soon need a coffin; he is not able to live a reciprocal experience, taking into account the feelings and reaction of his daughter. (That simple description of this eccentric behaviour is not enough to affirm the most probable father's blunting affect.) In other words, he is unable to comprehend; he does not participate in the other's life. He is dissociated from the others and from the circumstances: he is out of the common axis; he is an eccentric (Hojaij 1978, 1987).

Looking for some fundamental and permanent feature in the schizophrenic patient, Hojaij (1987), in a long-term study, investigated the possibility of a structural disturbance in the capability of comprehension ("understanding") in the schizophrenic patient. The work is related not to the "understanding" that the psychiatrist may or not may have about the schizophrenic phenomena, but how the process of comprehension presents itself into the schizophrenic, how the patient manages this process of intuitive knowledge. Comprehension is understanding as a natural capability to, through the intuition, immediately apprehend the whole situation, considering the total sequence of the events (from the past to the future) and to sit in the other situation through the empathy (transposition capability). After some point in life, the schizophrenic loses the capacity to discern the essential from the non-essential according to the general, and then is no longer moved by relations of common sense. The teleological sense is lost and the intuitive enfolding apprehension fails. The

chain of events in life does not follow the comprehensive spiral (progressive and broader knowledge), but causality laws. The transposition capability is damaged; in other words, the patient is not able to be in the place of the other person and then feel, think, live as if he was the other one; the capacity of loving is lost. The schizophrenic is moved by some part of the reality, not by the totality; he is attained at the current moment, not taking into consideration the continuous process of existence; he is here, but not living here; he is apart, may be delirious (out of the route). He is split (dissociated) from the reality as well as split (dissociated) from his own vital history. There is a complex rupture in the structure of the personality and in the vital history.

The notion of rupture is found in Jaspers (1977, 1997) and it is essential to distinguish the schizophrenic process from other similar psychopathological syndromes. Jaspers calls attention to the "something new" that happens in the psychic life of a schizophrenic: at some point of time something new and heterogeneous appears in relation to the previous personality; it is as if something strange has been inserted in the personality, or more precisely, something strange replaces, to more or less a degree, the original personality; from now on, the other becomes the one. The psychic life follows a different process, a schizophrenic process. The identification of this point of rupture - a radical transformation in the personality- is a very important element for the clinical diagnosis of schizophrenia (Hojaij 1985, 1987).

The same essential notion captured in the German authors about the split personality in schizophrenia is found in the French school, like in Chaslin *("Les folies discordantes"* 1912, cited by Minkowiski, 1966), de Clérambault (*"Automatisme Mental et Scission du Moi"*, 1920), Minkowiski (*"la perde de contact vital avec la réalité"*, 1927; 1966). In "*Le temp vécu"*, Minkowiski (1973) explains that in the schizophrenic there is a breach in the chain of the existential process; then appear the "acting without tomorrow", "frozen acts"; the things (all things) are disconnected, the things are more embodied than tasted.

Clinical forms

After Kraepelin had taken the forms hebephrenia (described by Hecker in 1871), catatonia (described by Kahlbaum in 1874) with paranoia to compose Dementia Praecox, he described 11 more sub-types: simples (from Bleuler), silly (hebephrenia), simple depressive (stupor), delusional depressive, circular, agitated, periodic, catatonia (excitement, stupor, melancholia attonita), paranoid gravis, paranoid mitis, confusional speech (schizophasia).

Bleuler (1950) added the form simples to the first group described by Kraepelin. On the other hand, Schneider (1959) just accepted the traditional simple, paranoid and catatonic; hebephrenia should be included in the simple, considering that if it begins in adolescence it presents the appearance of such age (pathoplastic significance).

The big step in discriminating new clinical forms to the group of schizophrenia and at the same time discriminating groups other than schizophrenia and manic depressive psychosis is attributed to Leonhard. Kleist largely influenced Leonhard during his years at the Frankfurt Mental Hospital. Leonhard (1999) has personally examined approximately 1450 schizophrenic patients. It is from this magnificent clinical experience that he developed the differentiation between the two groups and sub-groups of schizophrenia: "If independent sub-forms are differentiated, many ambiguities can be cleared" and discrepancies solved (1999). He separated schizophrenia in two groups: a) systematic schizophrenia (catatonia, paranoid and hebephrenia) and; b) assystematic schizophrenia (periodic catatonia, affective paraphrenia and schizophasia). The later group has a high genetic loading and a relatively good outcome. On the other hand, the systematic schizophrenias have a very low genetic loading (rare family history of psychosis) and a poor outcome.

A further schizophrenic syndrome was added by Kasanin (1933). He described a series of nine patients who had all been assigned diagnoses of Dementia Praecox. They had all demonstrated an acute onset of the disease that was followed by a relative rapid recovery. "Noting that the patients' symptoms represented a combination of schizophrenic and affective components, Kasanin suggested the term schizoaffective psychosis to describe these patients' disease. This category subsequently became part of the American concept of schizophrenia" (Neale and Oltmanns 1980). It should be discussed whether this group identified by Kasanin is composed of schizophrenic patients with intense mood symptomatology and relatively good outcome or bi-polar patients with intense productive symptomatology, and even if they are not part of the same group identified by Leonhard as having cycloid psychosis, or a group of patients having a temporal lobe epilepsy.

Huber (1971), a Schneider disciple, based in the study of 50 patients (pre-pharmacological era) describes a new sub-type: cenestesic schizophrenia. Usually, the cenestesic phenomena are mentioned as prodromal phase or accompanying other symptoms that dominate the clinical picture. Under the designation of cenestesic schizophrenia there

are syndromes characterised by abnormal experiences in bodily sensations, many autonomic, motor and sensorial symptoms that follow during all the course of the disease. The cenestesic symptoms have a peculiar feature of continuous movement, changing in the presentation, in the course (phasic, paroxistic) and in a spectrum that goes from a hypochondriac configuration to body hallucinations with passivity experiences (Bacci and Hojaij 1984). A few authors make reference to this form described by Huber, perhaps due to the fact that they do not present the so well-known first-rank symptoms. The almost complete absence of the classical symptoms makes the cenestesic schizophrenia misidentified as a hypochondriac (neurotic or depressive) syndrome, psychopathic personality, epilepsy, etc. (Bacci and Hojaij 1984).

Crow and Carpenter carried out another attempt in the exploration of subtypes. In 1980 Crow pointed to what he described as the "paradox" of schizophrenia. Computerised tomography studies revealed structural brain changes in some patients with schizophrenia. Yet, there was evidence also of a neurochemical disturbance, since schizophrenic symptoms often responded to antipsychotic medications. To resolve the paradox, Crow (1980, 1982) proposed that two syndromes can be distinguished in schizophrenia and that these are related to different underlying pathological processes. The concept is not that there are two separate diseases, but two separate components to the disease process; in a particular patient at one point in time, one or other processes predominate or both may be present (Crow 1986). He proposed that positive symptoms (abnormal psychological features such delusions, hallucinations, and thought disorder) be labelled the Type I Syndrome, while the negative symptoms (diminished or absent normal functions such as flattening of affect, poverty of speech, and loss of volition) be labelled the Type II Syndrome. "The importance of this distinction is that the two syndromes predict different things. Specifically the presence of the Type I Syndrome predicts response to neuroleptic drugs, while the presence of the Type II Syndrome predicts poor long-term outcome irrespective of drug treatment. Because they appear to represent separate dimensions, I suggest the two syndromes be related to distinct pathological process: disturbance of dopaminergic transmission being related to the drug responsive (the Type I Syndrome) and a quite separate and perhaps encephalitis-like process being associated with the Type II Syndrome" (Crow 1980).

Further defining the typology, Crow and colleagues (1980, 1982, 1985) characterised Type I as having acute onset, usually normal intellectual function, normal brain structure, good response to antipsychotic drugs, possible increase of D2 dopamine receptors, and the absence of negative symptoms. In contrast, Type II schizophrenia is characterised by insidious onset, intellectual deterioration, enlarged cerebral ventricles, poor response to antipsychotic drugs, and prominent negative symptoms (Crow 1989).

It should be considered that those schematic ideas regarding the two subtypes of schizophrenia (Type I and Type II) do not exist in clinical practice. Many times in the same patient there is an overlap between the two kind of symptomatology referred to the subtypes, and there is no cerebral evidence of anomaly in patients with deteriorate symptomatology. Other very important observations to contest Crow's theory are: the so-called new antipsychotics (such as clozapine, olanzapine, etc.) do promote a significant reduction of negative symptoms and a significant improvement of all personality aspects, some sort of a (partial) psychopathological recovery.

Carpenter and colleagues (1988) refined the typology of negative symptoms by providing a rationale for distinguishing the primary, enduring negative symptoms of schizophrenia (termed deficit symptoms) from the more transient negative symptoms secondary to other factors. For instance, a social withdrawal is not always a direct measure of negative symptoms. Additionally, behaviours and inner experiences that are postulated to be negative symptoms may be either primary or derivative. "The clinician, when encountering putative negative symptoms, such as apathy, avolition, anhedonia and anergia should attempt to discern whether factors such as drug effects, dysphoric mood, self-protective reduction of stimulation are causative. It is important to differentiate derivative or secondary negative symptoms from those that are primary or direct expressions of a pathologic dimension of schizophrenia. The treatment and course of secondary negative symptoms are expected to be responsive to temporal changes in the factors with which they are associated," they added. In another sense, Carpenter and colleagues are replaying the old and useful German concepts of "pathogenic and pathoplastic".

These concepts "pathogenic and pathoplastic" were developed by Birbaum (cited by Leme Lopes 1980) in his "structural analysis", to differentiate what was directly related to the psychosis from others not directly related and non-essentials for its determination: "The psychosis is a complex with specific structure. The symptomatological arrangement is recognised by pathogenic factors (specific

aetiology) and pathoplastic factors (disease's configuration, special design of the presented psychosis)" (Birbaum cited in Leme Lopes 1980). The personal characteristics and circumstances (pathoplastic elements) have a significant contribution in the presentation, giving the "colour" of the psychosis, many times the more attractive and appealing phenomena.

Beyond consideration of positive and negative symptoms in schizophrenia, both Huber (1990, 1995, 1996) and Gross (1996) have emphasised basic symptoms (defective symptoms). Basic symptoms are defined as self-experienced affective-cognitive deficiencies reported by the patients. Basic symptoms appear as prodromal phase, lasting 3 years. Through a personal investigation composed of 1800 schizophrenic patients, Huber emphasised the importance of diagnosing schizophrenia in its early stages before the first clear psychotic episode. Founded in Prodromes and Outpost Syndromes, determined by basic symptoms, Huber and Gross et al (1987) have developed a standardised survey of basic symptoms in the Frankfurt Questionnaire and the Bonn Schedule for the Assessment of Basic Symptoms. The richness of the Bonn Scale and its effectiveness in terms of diagnostic tool are still awaiting international recognition.

A similar approach, looking for "minor" symptoms (such as anhedonia) in schizophrenia, was developed by Chapman and Chapman (1980).

There is no doubt as to the long evolution of schizophrenia and as to its definition as an illness that touches the whole personality. What has not been well determined yet are its clinical forms and types of outcome. The developments proposed by the authors who followed Kraepelin did not come to a consensus, and many of the sub-types described do not appear to be completely delimited. Although it is possible to differentiate many types of clinical arrangements and evolutions, it is not possible, until now, to predict the outcome of a specific patient (Schmid et al 1991). On the other hand, the different types of evolution very often confuse even the most experienced psychiatrists and do not allow an appeasing acceptance of a nosological unit.

Natural history

Part of the disagreement over core symptoms, boundaries and course emanates from a reduced emphasis on the natural history of schizophrenia. In terms of Dementia Praecox, the knowledge of the natural course was given by studies which began systematically in the last century in the French and German schools. Jaspers' (1977, 1997) studies characterising schizophrenia as a Psychic Process, a basic difference between the primary delusion and the secondary delusion beginning with the study of the structure and content of the delusion, the distinction of Schneider's first and secondary rank symptoms, the distinction of Leonhard's several clinical forms, the phenomenological studies by Conrad (1958), Huber's (1995, 1996) prodromic symptoms, etc., were all established from a natural vision of the illness. The concept of a bad prognosis of schizophrenia, its incurability, was determined by longitudinal studies with almost no therapeutic intervention. This natural vision of the illness is either captured directly as the disease progresses, or in a retrospective vision by means of anamnesis. Being a chronic illness, the understanding of schizophrenia can only be achieved through a historical personal perspective. How does schizophrenia begin? What are its evolutionary forms? Is it possible to establish a schedule for its clinical forms? Do they follow any criterion, or do they present themselves at random in each patient? Is it possible to establish a prognosis according to the type of beginning, as it is usually said: acute beginning, good prognosis; insidious beginning, bad prognosis? Or establish a prognosis according to the clinical type?

In the schizophrenic syndromical universe there are significant differences in terms of beginning, course and outcome. What leads to a stabilisation of the disease, a not so intense personality disintegration such as we find in some paranoid psychosis, or to a good outcome through hypomanic, manic or depressive episodes such as in some hebephrenia? Is it possible to compare an akinetic catatonia to a paranoid-hallucinatory schizophrenia? What can be said about the patient's having a certain clinical presentation at the beginning, and then another one, returning to the previous, etc? The symptomatological arrangements (syndromes) identified as hebephrenic, paranoid, catatonic, etc., seem to be not really types or forms of schizophrenia, but states (clinical states), transient states, of just one psychopathological unity.

Is there really an acute beginning in schizophrenia, or only a progressive acuteness (explosion of pseudo-hallucinations and primary delusional experiences, or catatonic states, or a highly stressing delusional mood) of a process which is being brewed for some time? Authors such as Weitbrecht (1970) and Huber (1995) observe a gradual beginning of the psychosis, which could extend for months or years, with a relative social adaptation. In many cases, over many years delusions and hallucinatory experiences are encapsulated; psychopathological signs would only be identified at the personality level. As it is known, these signs are often only considered as personal extravagances. Other symptoms, such

as Huber's (1995) prodromic symptoms, can extend for years without interfering significantly in the life of the patient, or leading to medical identification. Häfner (s/d) identified a gap of more than four years between the onset of schizophrenia and first-time hospitalisation.

Often the beginning of some gradual process is very rich in experiences of strangeness in relation to the self (depersonalisation) and the world (derealisation). Sometimes it can be a particular mood (delusional mood of Gruhle) with vague feelings, no clear suspicions, or obsessive-compulsive phenomena with experiences of strangeness, perplexity, delusional ideas of influence and end of world. Some patients live a strange gradual dissolution of the personality, a progressive feeling of uselessness and powerlessness. In some other cases of a more rapid explosion of the schizophrenic process, the patients notice themselves submerged and possessed by a gigantic complex of delusions and hallucinations developed in an atmosphere of intense agitation or beatific serenity (Hojaij 1985).

Conrad (1958) gives a very impressive description of the beginning of the schizophrenic process in his book *"Incipient Schizophrenia"*. Studying 117 male soldiers (1941-1942) with recent first episodes, Conrad defines a detailed structure and process for the schizophrenic experience:

1. trema (prodomal phase: anxiety, threatening, fears, feelings of guilt, sinfulness, hopelessness, thought blocking, feeling of dissolution, suspicions, self-absorbed)
2. apophenia (consciousness of abnormal meaning to everything: delusions)
3. anastrophe (consciousness that everything is related to the patient)
4. apocalipse (catatonic behaviour);
5. consolidation (gradual reduction of the level of symptoms and some adaptation to them)
6. residual (loosening of will, impulse to life). It should be mentioned that an epidemiological analysis of Conrad's work has been performed by Hambrecht and Häfner (cited by Häfner, s/d) partially validating his findings.

The Iowa 500 Study (Winokur and Tsuang 1996) is a modern and controversial naturalistic longitudinal approach to schizophrenia (and depression and mania) touching many of the important aspects pointed out in this paper.

Undoubtedly, the restoration of anamnesis is essential - it has characteristics of revealing the entire peculiarity of each patient, and can by no means can be substituted by structural interviews. The dilemma is how to find a way of returning to the peculiar anamnesis and guarantee the objective proposed by the standardised interviews.

Diagnosis

In relation to the diagnosis of schizophrenia there are still all kinds of conflicts. All the extraordinary technological advances of cerebral investigation have, to date, not been able to get close to the truth of schizophrenia. Sometimes there is an impression of "shooting at random", trying to come across fortuitous cerebral findings which then might be related to the schizophrenic symptomatology. The fact is that, as the laboratory investigation is not forestalled by a correct clinical investigation, by rigorous psychiatric propaedeutics, all and any findings will be the object of mere theorisation without underlying principles (Hojaij 1995). It is evident that this scission between the clinical reality and the basic investigation contributes to many frustrated attempts at understanding schizophrenia. The same call has been recently made by Andreasen (1998): "Therefore, we need to make a serious investment in training a new generation of real experts in the science and art of psychopathology. Otherwise, we high-tech scientists may wake up in ten years and discover that we face a silent spring. Applying technology without the companionship of wise clinicians with specific expertise in psychopathology will be a lonely, sterile, and perhaps fruitless enterprise."

Following Schneider (1959), it is not possible to say "this is schizophrenia" (at his time and until now there has been no clear somatic data), but just "this is currently designated schizophrenia". There is not a positive and conclusive statement on the clinical diagnosis of schizophrenia as a disease. The classical medical diagnosis (encompassing aetiology, pathogenesis, clinical picture, etc.) cannot be currently reached for schizophrenia. The diagnosis is just under the psychopathological level, and sometimes a fluid and vague impression to be further confirmed by means of a detailed phenomenological investigation. All the tentative steps to reach a consensus in terms of diagnosis for schizophrenia crashes into the absence of definite somatic base and into the kaleidoscopic richness of this intricate phenomenon. At the end there is always a diagnosis for close estimation.

Which is the best approach for the diagnosis: the clinical form, that is, a set of symptoms, or types of outcome? From a strict clinical point of view it is necessary to combine the cross-sectional examination of the symptomatology with the long-term observation (via anamnesis and/or via direct follow-up). As a process, schizophrenia must be grasped in longitudinal perspective, and as an illness suffered by someone must be apprehended immediately through the mental state examination.

Schizophrenia is considered a splitting illness, a splitting process, a splitting structure, a splitting person, a person split from his own original vital history, a person split from the common world. If this particular issue is taken into account, a descriptive phenomenological criterion from classical authors (despite some personal differences) is still necessary to give some certainty in terms of diagnosis. Thus, there will be comparison not just of clusters of symptoms, but complete clinical pictures with their whole sense.

It is not intention of this paper to go into a discussion about the structured interviews and the operational diagnosis. For the diagnosis of schizophrenia, in the absence of biological markers, the importance relies, most of the times, on symptoms of a qualitative and subjective nature. On the other side, the measurement (it does not matter how well constructed a structured interview is in terms of reliability and validity, how excellent are the operational definitions) will always be executed by a person. There is a direct proportionality between the number of "somatic symptoms" and reliability in a way that organic and psychotic disorders have higher reliability than neuroses and personality disorders (Kendell 1992). Thus, if the assessment is not made by an experienced researcher, able to detect sometimes a sophisticated psychopathology, the result will be restricted not by the rating scale but the clinician. Kendell (1992) advocates the use of the structured interviews by "skilled hands", and alerts that "clinical judgements, whether they concern depersonalisation or bronchial breathing, are inevitably imprecise and imperfect, and the best we can do is to understand what the problem are and do our best to minimise them."

The so-called operational diagnosis has not been able to offer a solution, and what happens is almost a neglect of the patient. There are diagnoses of questionable validity based on questionnaires tested in origin by non-psychiatrists (DSM-III 1980) trying to accommodate the patient within some diagnostic box. These sorts of diagnostics are often simplistic (although including some classical concepts) made by a descriptive behaviourist and are of a statistical nature, leading to classifications (ICD-10 1992 and DSM-IV 1994) composed by a strange and incompatible mixture of symptomatological, syndromal and etiological structures (Hojaij 1994). One cannot leave aside the fact that some researchers who are tied to modern classifying systems (DSM and CID types) may be determining limitations and distortions in clinical research.

To surpass this impasse in the area of diagnosis, psychopathology must be reintegrated in psychiatric research and practice. There is a need to rehabilitate the phenomenological description which admits the wealth of special inner experiences, the same phenomenological description that originated the definition of Bleuler's (1950) fundamental symptoms and allowed this author to create the term schizophrenia, or Schneider's (1959) first-rank symptoms, or which allowed Jaspers (1977) to elaborate the idea of Psychic Process, or Binswanger (1972) penetration into the intimate living of the schizophrenic. From the psychiatrist side, Weitbrecht (1970) uses the expression "schizophrenic atmosphere" to be apprehended by the experienced clinician. Should the "precocious feeling" by Rümke (1942) be put aside when facing a lack of spontaneous, non-reflexive, naive happiness? Or a cold, indifferent, self-engrossed, non-spontaneous, affected, formalistic, rigid, pompous (paranoid) person? The great challenge for psychopathology is to transform all the subjective data elicited from the patient and the others by the experienced psychiatrist (like the precocious feeling) into objective and shared data. This is a task for many psychiatrists, for many years.

The investigation of schizophrenia cannot be developed without the observation, intuition, knowledge and experience of the psychiatrist. Therefore, as in the rest of Medicine (and life in general) the aptitude for diagnosis develops along with the clinical practice, and the identification of complex entities is sometimes - one most admit - reserved for the most experienced.

Apropos, this quote from Schneider (1959): "Experience show us that it is often difficult to establish a psychiatric diagnosis from a psychopathological finding. In this case, it does not mean from the beginning, to add and combine symptoms perceived and demonstrate objectively, as in a somatic diagnosis, but of a judgement of manifested life experiences, of an evaluation of behaviour and of attitudes of the patient and the consideration of the impressions of the examiner." Leme Lopes (1980), commenting on the great challenge that is the diagnosis of schizophrenia, said: "To work with such a vast keyboard one has to be a good player. And this is an ability which can only be progressively attained while one practices this difficult science which is Psychiatry".

A great responsibility in the diagnosis process lies on genetic studies, not only of family lineage, but mainly those related to the study of gene anomalies. Interestingly, epidemiological conclusions (Häfner 1991; Jablenski et al 1992) are concordant in relation to the worldwide distribution of schizophrenia, pointing out the relevant genetic factors that should blow up in genetic research. Hopefully, accurate genetic

findings will be able to provide an explanation for the cause of schizophrenia and help in the prevention and treatment; but maybe not provide an understanding of the symptomatology and the whole and absolute transformation of the personality. As Wyrsch (1957) said: "Everything indicates that the disorder occurs where a person is contained as a single unit, where the psyche arises, and where the spiritual person is possible. In this sense, schizophrenia is, among all the psychiatric illnesses, the one that can best be designated a disease of spirit (Geisteskrankheit).

Methodology

Are the methodologies used in the study of schizophrenia appropriate, or are we still living the precarious body-soul dichotomy, and therefore looking for motivations of all kinds (meaningful connections), or strictly matter alterations for the explanation (explaining methodology) of an illness which comprises the totality of the personality? It should be reinforced that the two fundamental psychopathological methods introduced by Jaspers (1997) do not exclude each other and should be used in a complementary way. In the current epistemological situation, a dialectic use of both methods brings the opportunity of going further into the neuroscience investigation related to and anticipated by correct phenomenological psychopathology. Since there is no unitary method for approaching the mentally disturbed human being, the two methods should be used appropriately to compose the best approximate picture.

Concerning the genesis of schizophrenia, should one speculate, dare and experience an area of research that would consider not only the neurotransmitter systems (Sokoloff et al 1995; Iqbal and Van Praag 1995) or specific cerebral areas (Taylor 1995), or certain enzymes such as for instance glutamate (Ebert et al 1995), or neuropeptides (Verhoeven 1995), but an area of research - considering the illness as having reached the totality of the person - such as the irradiating energy in the brain? (Popper and Eccles 1977). Should one look for more than an alteration of matter, try more than to relate motivational situations, distinguish, locate and measure energetic systems, or even further, consider an energetic meta-structure (Hojaij 1996a)?

Therapeutic evolutions

Through the effective introduction of modern therapeutic techniques, the observation of schizophrenia in natural evolution has been practically suppressed. The schizophrenics are all found (or almost all) maculated by therapeutics; symptoms are weakened or disappear (delusions and hallucinatory experiences), others appear directly promoted by drugs (neuroleptic apathy), and others as a consequence of neuro-pathological alterations (tardive dyskinesia). On the other hand, during the symptomatological course after an acute outbreak, symptoms of a depressive nature may occur which, for a long time, were not considered to be related.

Delay (1961) already commented about the transformation of symptomatology and the evolution of psychosis as a result of antipsychotics: "This transformation possibly represents the deepest and true 'revolution' due to the new therapeutic method". Therefore this has increased the cases of the so-called incipient schizophrenia and residual schizophrenia. Delay, so long ago alerted: "It is necessary to have great patience and a solid clinical experience to distinguish banal symptoms of asthenia from lack of concentration, instability or professional maladjustment from those due to a psychosis or neurosis, or even a problem of medication. The classical 'macroscopic' symptomatology tends to be substituted by a finer symptomatology..."

However, in the last four decades a certain therapeutic enthusiasm has been observed. The so-called antipsychotics present an ample spectrum of clinical action and are handled relatively easily, thus giving chance to a ready therapeutic intervention. This intervention ends up erasing the clinical picture of psychosis before the diagnosis is completed. If the use of antipsychotics is in larger doses than those suitable for that patient in particular, the pharmacological blot reaches a dimension that surpasses the symptomatology of the psychosis: the totality of the psychic life ends up by deteriorating. Consequently, this untimely therapeutic intervention may be one of the factors responsible for why the exact knowledge of schizophrenia has progressively been lost in the last decades. There is no doubt that a quick therapy is necessary, specially knowing that a precocious beginning in the treatment of schizophrenia, in general, allows a more favourable prognosis. However, the dramatics of the clinical picture must not correspond to a violent intervention.

It may be said that the traditional antipsychotics (it is too soon for a statement concerning the novel antipsychotics) do not touch the essence of schizophrenia:

1. they act as a temporary solvent-delusion and hallucination
2. they gradually erode (not completely) the psychosis, allowing certain return of the natural life categories (Hojaij 1987)
3. they permit some return of the personality modulation, but not to a completely recovery
4. they promote a change in the schizophrenic psychopathology, the main evident

symptoms are abolished and the fundamental psychotic structures like pure defect (Huber 1972) and comprehension disturbance (Hojaij 1987) start to appear more clearly.

Endogenous psychosis
Treatment resistance of endogenous psychosis derives from the lack of knowledge of aetiology as well as from the restricted efficacy of current therapeutics. In spite of the great progress made since 1952, and particularly the introduction of the so-called atypical antipsychotics, the schizophrenic reality resists treatment, or is revealed in a greater or lesser degree of affective-volitional dullness, or in personality disorders.

Some interesting questions should be considered: In which way do the antipsychotics modify the psychopathology of schizophrenia? Which symptoms remit or simply reduce their intensity and remain during the entire course of the psychosis, and which of them resist current therapeutics? Which are the most favoured clinical forms? Can new determined pharmacological clinical subtypes be defined? Which are the long-term therapeutics effects observed? As regards the current drugs, is it possible to suppress the antipsychotics after a certain period of use? (Johnstone 1991). Does the delusional nucleus disappear completely? Are new types of "defects" coming up with current therapies? The investigation should be open to look for new symptoms that could come up during the treatment, besides those of neurolepsy itself.
Since there is a no complete psychopathological resolution due to psychopharmacotherapy, the symptomatological cleaning by means of antipsychotics should lead to a more profound investigation of the most original (or resistant) schizophrenic symptomatology. Perhaps, from this perspective, the psychopathological research continues to progress and directs itself to the core and essence of psychosis (Hojaij 1987).

The social-cultural influence
Forms of social organisation in the last decades, with life predominately in big cities which favour anonymity, offer a favourable field for the easy mimetic of schizophrenics in marginal groups, or the acceptance of their extravagances due to the loosening of social values. In one way or another, this may influence the diagnosis, and thus the indices of incidence and prevalence can be underestimated. On the other hand, it is important to verify up to which point the intense social factors, with current characteristics of rapid transformation and great pressure on individuals, only remain as pathoplastic factors with no direct interference in the form, course and evolution of schizophrenia. Considering the advances of modern biology and evolutionary theory it is valid to hypothesise that some genetic mutation is forced by significant and persistent social and cultural factors. Apart from vulnerability issues (Häfner 1991) the researchers should be prepared for a structural change in schizophrenia reflecting its symptomatology, evolution and results to treatment.

It is necessary to take into consideration "ambulatory schizophrenia" in opposition to an "asylum schizophrenia" (or "hospital schizophrenia"). The deteriorating pictures of bygone days have given place to pseudo-psychopathic forms, with significant relief of the productive symptoms. Today, the patient is always demanding, social life is much more intense, professional life is very diversified in big cities, which permits a relative adaptation of schizophrenics, and accentuated non-deterioration (just a psychological character of dullness). A great number of them are capable of social readjustment and re-establish, to a greater or lesser degree, work productivity.

The acknowledgement of "ambulatory schizophrenia" compels the question: Is schizophrenia today, studied in an outpatient service, identical in its clinical forms and evolution to schizophrenia classically attended and studied in hospital?

To go beyond
For one hundred years the history of psychiatry has evolved around schizophrenia. How is it possible that a certain psychopathological syndrome, so fundamental to the human being, has not been disclosed yet? How many thousands of studies of all kinds have been looked up in all the libraries of the world without ever having reached the necessary precision in conclusions? How have the researchers treated Dementia Praecox over these 100 years? What should be done from now on? (Hojaij 1996b).

Schizophrenia still needs a theory. It is an excellent field to conceive from the perspective of an evolutionary (Crow 1995), neurodevelopmental (Weinberger 1995), neurophysiological (Pantelis et al 1996; Pantelis & Brewer 1996) disease. In methodology, the object of study, schizophrenia, is completely different from all other psychiatric syndromes such as Major Depression, Organic Psychosis and Personality Disorder, in the sense that it is innovative and absolutely transforms the whole personality. It is a special condition of the human being. From an evolutionary and integrative conception (Popper and Eccles 1977; Eccles 1979; Eccles 1992) the schizophrenic could be considered a being (human being) with a disturbance of consciousness, a disturbance of self-consciousness. Considering

that all organisms have a purpose (intentionality) in their actions (von Üexkull cited in Hoff 1955), the person considered schizophrenic is making use (for some unknown reason) of non-common associations of neuronal systems. Perhaps the problem would not strictly be in the central-neuronal-system, or in the brain specifically, but in the way self-consciousness makes use of these neuronal systems. The music is no longer good - not because the music itself is not good or because the musicians are bad now, but because the conductor (the self-consciousness) is not all right. A deeper study of the self-consciousness, with new methods and techniques looking for the energy in the brain would be an interesting and challenging proposition. No matter the method, the original apprehension will come from the psychopathological approach.

Improvements to the studies of the predictors (Parnas and Mednick 1991) and early recognition of schizophrenia (Gross et al 1992; Huber 1995; McGorry et al 1996) are still needed, under the idea that precocious diagnosis means early treatment and better outcome. But there is also a need for long-term studies, since the disease has, until now and despite the many good social outcomes, an irreversible character. That perspective will help to in the search for a real anti-schizophrenic drug (not an "antipsychotic" that acts only symptomatologically), a drug that goes into the disease and may be some kind of drug that deals with the energy in the brain.

A pattern of mental illness, or a radical transformation of the human way of being, schizophrenia remains an enigma from the medical point of view. A hundred years of clinical investigation and cerebral explorations have not been enough to elucidate the real sacred illness. Only the united efforts of experienced clinicians and basic researchers with a clinical vision may bring the answers related to the origin and essence of schizophrenia. And when that time comes true, psychiatry will lose plenty of its charm.

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CASE REPORT/CASE SERIES ▸

Psychopathological Changes Preceding Motor Symptoms in Huntington's Disease: A Report on Four Cases

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Summary
Neurodegenerative disorders often exhibit "classical" psychiatric symptoms as an initial presentation of the disease. Here we present four patients with different psychopathological abnormalities who were later diagnosed as having Huntington`s disease. The range of symptoms covered affective and psychotic symptoms, antisocial behavior, cognitive problems reminiscent of dementia and suicidal idealisation. The pattern of progress of neuronal degeneration may be helpful in explaining the antecedent manifestation of psychiatric symptoms.

Key-words: *Huntington`s disease, neurodegenerative disorder, psychiatric symptoms.*

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Psychotic symptoms often precede neurological diseases, e.g. Parkinson's disease, Lewy body disease, Alzheimer's disease, amyotrophic lateral sclerosis or Huntington`s disease (HD)[11]. HD was first described by CO Waters (1841) and named after G Huntington (1872), who defined it versus Chorea minor as an hereditary disease. HD is an autosomally-transmitted, progresssive neuropsychiatric disorder, with its manifestation usually peaking in the 4th and 5th life decade. The so-called Huntington gene has been located on the short arm of chromosome 4, and the rate of repetition of a CAG triplet correlates with the clinical manifestation of the disease. HD's best known clinical features are bizarre movement disorders, mostly choreatic dyskinesias.

However, it has been estimated that 50% of patients with HD initially present with a variety of psychiatric symptoms or syndromes instead of motor symptoms [5], such as personality changes, impulsiveness, sexual aggressiveness [6], severe psychosis [7] and affective disorders [5;6]. Besides mental and cognitive phenomena [3;4] suicidal idealization can be prominent. These full-blown syndromes or at least marked symptoms can be noted in the cases described here, where psychiatric abnormalities preceded gross neurological symptoms, but finally led to diagnostic procedures verifying the diagnosis of HD.

Case reports

Case 1

A 28-year-old male car mechanic was admitted to our hospital with a depressive and lethargic syndrome. Until $1^1/_2$ years prior to admission he had had no psychiatric abnormalities and was socially well integrated. He then started to neglect social contacts and dropped his job. In addition, he showed loss of inhibition and exhibited unusual eating habits, such as refusing to eat alternating with binge-eating attacks. Since developing kleptomania one year prior to admission, he had felt persecuted and telepathically controlled.
At hospitalisation, apart from a spontaneous nystagmus with aim-directed hypermetric saccades, the patient showed no neurological abnormalities, and especially no movement disorders. A magnetic resonance imaging scan (MRI), liquor, touch and visually evoked potentials were without any pathological

correlates. However, in cognitive function tests he only reached a score of 25 in the mini mental status (maximum 30), which corresponds to slight cognitive impairment.

The family history revealed that the grandfather, the father, two uncles and one cousin from his father's side had abnormalities consistent with HD. Consequently, a molecular genetic testing was performed, which confirmed the presumptive diagnosis of HD.

Combined treatment with haloperidol (6mg/d) for the psychotic symptoms and baclofen for the nystagmus led to a satisfactory control of symptoms.

In summary, the patient had a high genetic load with paternal transmission, which is related to an early onset and rapid deterioration [8]. In line with this, he obviously developed cognitive symptoms quite rapidly. Otherwise, he presented with symptoms of loss of inhibition, including eating disorder and kleptomania, which are linked to a frontal pathology. Additionally, apathy and paranoid symptoms were observed.
It is rather questionable that the nystagmus was related to HD. The patient reported having had this symptom since youth. Other than this, no neurological abnormalities were observed. The nystagmus also responded quite well to baclofen. Gabaergic drugs have been tested in HD. Although baclofen inhibits the release of glutamate and aspartate, it was not capable of slowing down the progression of the disease [10].

Case 2
HG, a 55-year-old male bus driver, was admitted to our hospital for the first time after he had attempted to commit suicide by trying to cut his throat.

After being divorced from his wife 2 years previously, he developed a depressive syndrome and was consecutively treated with amitriptyline. In the last months before admission, he caused a number of accidents while working. He seemed to have difficulties in calculating distances and took wrong driving routes.

At admission, prominent symptoms were a severely depressed mood, concentration and memory impairment and psychomotor retardation. In addition, he mentioned sleep disturbances with early morning awakening and obsessive rumination about his private social situation. In summary, he had sufficient symptoms for the diagnosis of a major depression.

However, GH also described intermittent oro-facial fasciculations, and sporadic and involuntary deviations of his steps which had been occurring for 6 months.

Careful observation and neurological examination revealed athetotic movements of the torso, slightly dysarthric and slowed speech, ataxia with voluntary motion. Muscle reflexes were increased, partly cloniform and more pronounced on the right side. There were no pyramidal signs. In addition, he had hypometric saccades when moving his eyes, which were more pronounced towards the right, and a slight paresis of the convergence response. When he put out his tongue, singular involuntary moves could be observed.

Liquor, touch and visually evoked potentials were without any pathological correlate. The MRI revealed an atrophy of the cortex and the medulla, with plaques in the periventricular and thalamic region.

As it turned out, his mother and two aunts had died in their early 50s from a neurological disorder.

Consecutively, we performed a molecular genetic diagnostic test, which was positive for HD.

In summary, the patient had a maternal transmission of the disease, which usually correlates with late manifestation and higher incidence of personality disorders [8;13]. According to the patient, the depressive syndrome had already persisted for $1^1/_2$ years before decent neurological symptoms became apparent. These were not even very marked at the time of admission. Besides signs of global brain atrophy and possible spots of gliosis (which may, of course, also be vascular white matter lesions), the MRI gave no specific hint of HD. As we will see in a later case, functional imaging may be more sensitive in early stages of HD.

Case 3
The 52-year-old teacher was admitted to the Department of Gynaecology for hysterectomy. When her history was taken she reported suffering from depression for one year and that this had made her unable to work for the previous 6 months. Since then, she had been on fluoxetine treatment without any significant changes of symptoms. However, she complained of increasing restlessness which had been interpreted as either agitated depression or a fluoxetine side effect. Psychiatric counselling was organised by the treating physician.

At first psychiatric examination, she exhibited a formal thought disorder not typical for depression, partly with associative loosening, followed by ambiguity. Her basic mood state

closely resembled what is characterised as a mixed state in bipolar disorder, with the concurrent manifestation of depressive and (hypo)manic symptoms. In general, she appeared emotionally very labile and partly inadequate. She also had cognitive impairment untypical for depression and was not able to perform serial subtraction of 7 from 100, although she had still been working as a teacher until recently.

Her own history revealed that she had had to quit her job due to continuous struggles with her students' parents on educational matters, where she was not able to compromise. The family history again gave evidence for an inherited disease, since her father died aged 72 after years of immobility and inability to care for himself. Finally, he also appeared demented. She also reported that her sister was "nervous" and had to move around all time.

While her history was being taken, continuous movements, which appeared involuntary but were partly integrated into voluntary movements, became apparent. Otherwise, no abnormal focal neurological signs were detected.

Fluoxetine was discontinued without any changes in either psychiatric or motor symptoms. The consecutive genetic testing confirmed the diagnosis of HD.

In summary, this patient's pathophysiological syndrome showed elements of a mixed state concerning her mood, and signs of cognitive impairment with a recent and rapid onset. The discrete movement disorders had previously been interpreted as agitated depression or fluoxetine side effects. Motor signs of HD are, especially in early stages, quite variable, and without the typical choreatic dyskinesias. They may also resemble a generalised motor agitation that can be mistaken as a sign of depression or a drug side effect.

Case 4

This 42-year-old lady was admitted for suffering paranoid ideas and consecutive social isolation had started four years previously. She also experienced increasing apathy and anhedonia. On admission, she had marked symptoms of what is commonly seen in paranoid schizophrenia, including fear of persecution, formal thought disorders, depersonalisation, lack of energy and suicidal idealisation. Furthermore, concentration and memory appeared diminished.

The neurological examination showed no pathological findings.

Neuroleptic treatment led to an improvement of her paranoid symptoms, although the other symptoms remained. The suspicion was raised of a very early onset and atypical course of dementia. Psychometric testing revealed an IQ of 46, although this finding was hard to interpret due to language problems (her native language was not German).

Her family history revealed an early death of her father after several admissions to psychiatric hospitals, although the reason remained unclear. Her brother also suffered from a "psychosis", and her daughter had already attempted suicide twice.

The CCT showed a generalised but mild atrophy of the brain, with a small defect of the left pallidum. However, the FDG-pet scan revealed a marked hypometabolism of the whole basal ganglia area. Genetic testing finally confirmed the diagnosis of HD.

In summary, the patient had typical symptoms of paranoid schizophrenia, combined with a cognitive impairment which may be untypical for a sole schizophrenia. She had no focal neurological signs when examined. Despite the lack of neurological signs, her basal ganglia were already severely impaired from HD, as detected by FDG-PET.

Discussion

Whereas paternal transmission appears to correlate with an early onset and more rapid course of the disease [5], maternal transmission correlates with a higher incidence of primarily psychiatric symptoms [13]. Due to the relatively prolonged course of the disease, these symptoms may stand alone for a long time without any obvious movement disorders, and patients may be wrongly classified as "pure" psychiatric patients. Furthermore, distinct impairment of cognitive functioning can already be observed in gene carriers without any other neurological or obvious psychiatric impairment [9]. Cognitive impairment after manifestation of the disorder still appears to be somewhat specific: Comparing patients with Alzheimer's disease and HD with an identical score in the mini-mental state battery, HD patients perform worse in tasks requiring sustained concentration, e.g. serial subtraction of 7 from 100 [4]. In addition, skills such as planning, organizing and mental flexibility appear to be affected at a relatively early stage of HD [3].

Examining 186 patients with HD in the only population-based study of HD so far, Folstein [5] reported on a high incidence of psychiatric syndromes. Forty per cent of the patients suffered from affective disorder, with depression being more common than mania. This is in slight contrast to earlier reports which usually characterise manic symptoms as typical for HD. However, Huntington already described suicide

attempts as a prominent feature of the disease. Intermittent irritability, approximating what is described as intermittent explosive disorder in DSM III, was diagnosed in 31% of the examined patients in Folstein's study. A schizophrenia-like syndrome was observed in 6% of the patients.

In the course of the disease, a global atrophy of the brain develops with an average loss of brain weight of 250 g compared to controls [12]. The physiological function of brain structures that are primarily affected by HD may explain most of the psychopathological changes. The primary degeneration of the striatum starts from the medial caudate and proceeds laterally towards the putamen and globus pallidus. The primarily affected neurotransmitters are thus GABA and acetylcholine: However, the selective survival of type II spiny interneurons in the caudate also leads, via increased somatostatin synthesis, to an increased dopamine turnover. This, together with a relative hyperglutamatergic state due to loss of GABAergic neurons, may provoke psychotic symptoms in HD.

The extent of caudate atrophy correlates with cognitive dysfunction such as intelligence, memory and visuospatial deficits [2]. The loss of acetylcholine may play a prominent role in memory deficits, especially in the retrieval of memory, where acetylcholine is an essential neuromodulator.

As there is an extensive connectivity between the striatum and the prefrontal and parietal cortex [1], cortical dysfunction, including loss of inhibition and affective instability, may become symptomatic due to secondary degeneration of the cortical neurons. Bundles subserving neuropsychiatric functions such as cognition and emotions originate from the caudate and may be affected earlier than those of the motor circuits which connect with the putamen.

In conclusion, these cases with prominent psychiatric symptoms should remind readers of the importance of taking a thorough family history and neurological examination, including consideration of any distinct motor abnormalities that may be present.

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CASE REPORT/CASE SERIES ▸

Amantadine-induced multiple spike waves on an electroencephalogram of a schizophrenic patient

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Summary

Although amantadine is relatively free of side effects compared with levodopa, the incidence and severity of unwanted effects, such as hallucinations, insomnia and dizziness, markedly increase when the daily dose exceeds 200 mg. A 63-year-old schizophrenic female developed the Pisa syndrome following neuroleptic medication. She was started on a regimen of amantadine, 200 mg per day, on September 4, and the electroencephalogram (EEG) on September 11 was within normal limits. The dosage was increased to 300 mg on September 18 because there was no improvement and no side effects. Two days later a generalised convulsion occurred and an EEG revealed frequent multiple spikes or sharp waves with slow waves. No epileptic seizure has been observed since the amantadine was discontinued. The EEG on September 27 was again within normal limits. To our knowledge, the EEG of a patient with convulsion induced by amantadine has not been described previously. The epileptic mechanisms of amantadine have not been elucidated; however, it may be related to a modulating role of dopamine in the central nervous system.

Key words: *amantadine hydrochloride, dopamine, generalised convulsion, EEG, Pisa syndrome.*

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Introduction

Amantadine, with an unusual symmetrical structure, was initially introduced as an antiviral agent for the prophylaxis of A2 influenza (Davies et al 1964) and was unexpectedly found to cause symptomatic improvement in patients with Parkinsonism (Schwab et al 1969). The drug is clearly less efficacious than levodopa, but slightly more so than the anticholinergic drugs (Cedarbaum and Schleifer 1990). In addition to those effects, it has been suggested recently that amantadine plays a neuropsychiatric dopaminergic (DA)-stimulant role, accounting for improvement in alertness and/or mood in persistent vegetative states (Horiguchi et al 1990), senile dementia (Muller et al 1979) and multi-infarct dementia (Hirasawa et al 1984), accounting also for the alleviation of behavioural disturbances in traumatic brain injury (Gualtieri et al 1989) and for the reduction of perseveration (Imamura et al 1994). The changes in clinical features were associated with a decrease in slow activity and an increase in alpha activity on electroencephalograms (EEGs) (Muller et al 1979; Hirasawa et al 1984; Horiguchi et al 1990). Periodic discharges and slow-wave activity in patients with Creutzfeldt-Jakob disease were sharply reduced by amantadine, accompanied by an improvement in wakefulness and mentation (Terzano et al 1983). EEG improvement was also observed in young normal volunteers, who showed a decrease in slow activity associated with increases in higher alpha activity and lower fast activity, suggesting vigilance enhancing effects of amantadine (Suitsu et al 1992).

Although amantadine is relatively free of side effects compared with levodopa, their incidence and severity markedly increase when the daily dose exceeds 200 mg per day (Cedarbaum and Schleifer 1990). The most common adverse effects of the central nervous system (CNS) are dizziness, insomnia, impaired concentration, irritability, depression, and anxiety (Schwab et al 1969; Cedarbaum and Schleifer 1990). Severe CNS symptoms, such as disorientation and hallucination, have been described in patients on chronic amantadine therapy, especially those who receive the co-administration of anticholinergic agents that may exacerbate

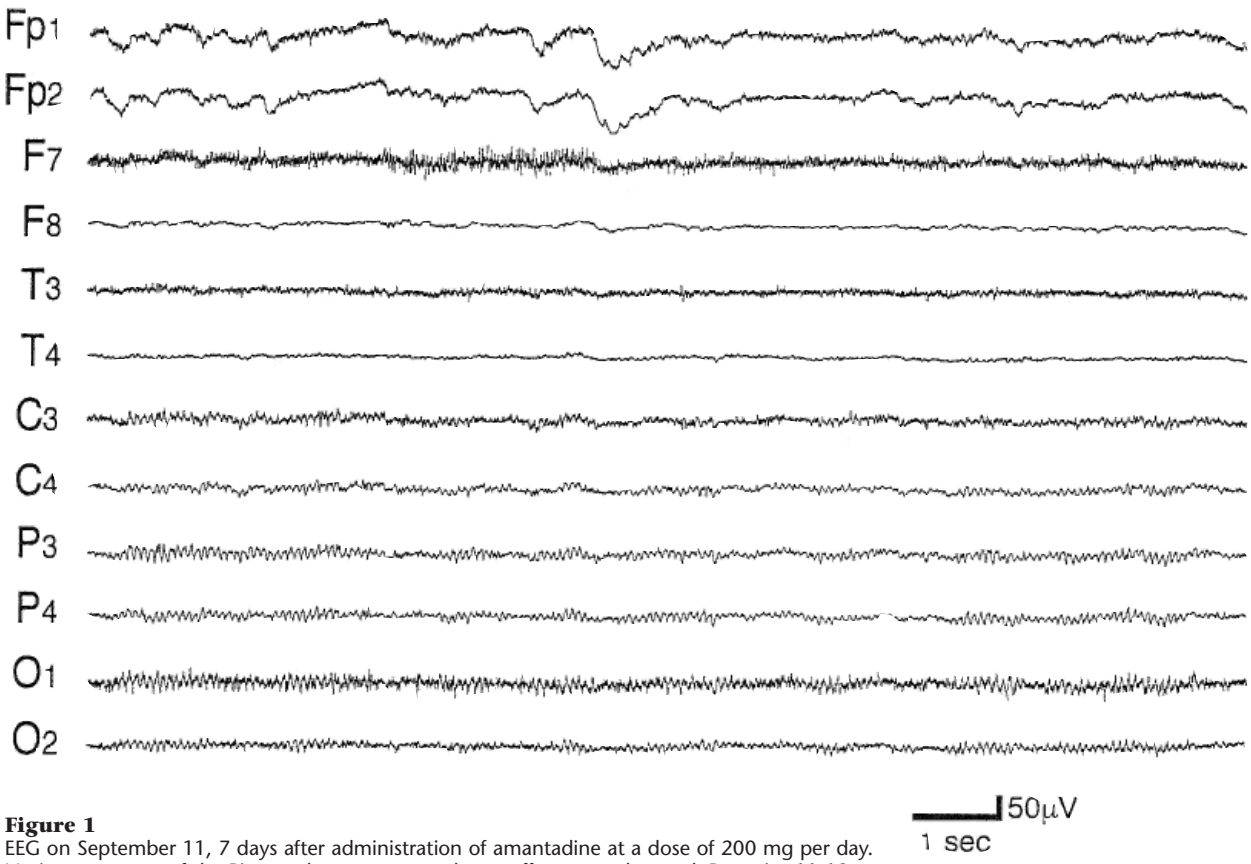

Figure 1
EEG on September 11, 7 days after administration of amantadine at a dose of 200 mg per day. No improvement of the Pisa syndrome, or any adverse effect, was observed. Posterior 11-12 Hz and 30-40 μV alpha rhythm was dominant and thought to be within normal limits.

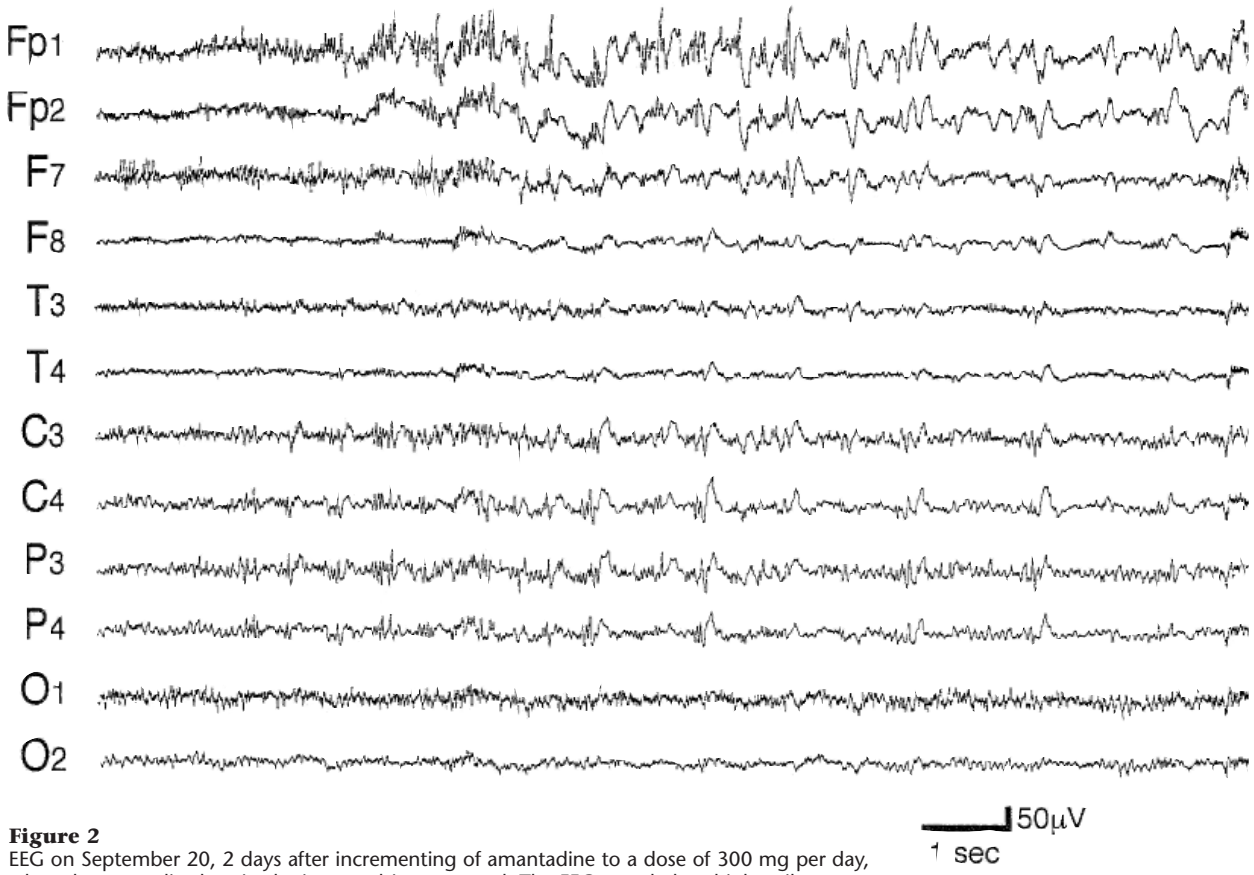

Figure 2
EEG on September 20, 2 days after incrementing of amantadine to a dose of 300 mg per day, when the generalised tonic-clonic convulsion occurred. The EEG revealed multiple spikes or sharp waves with slow waves.

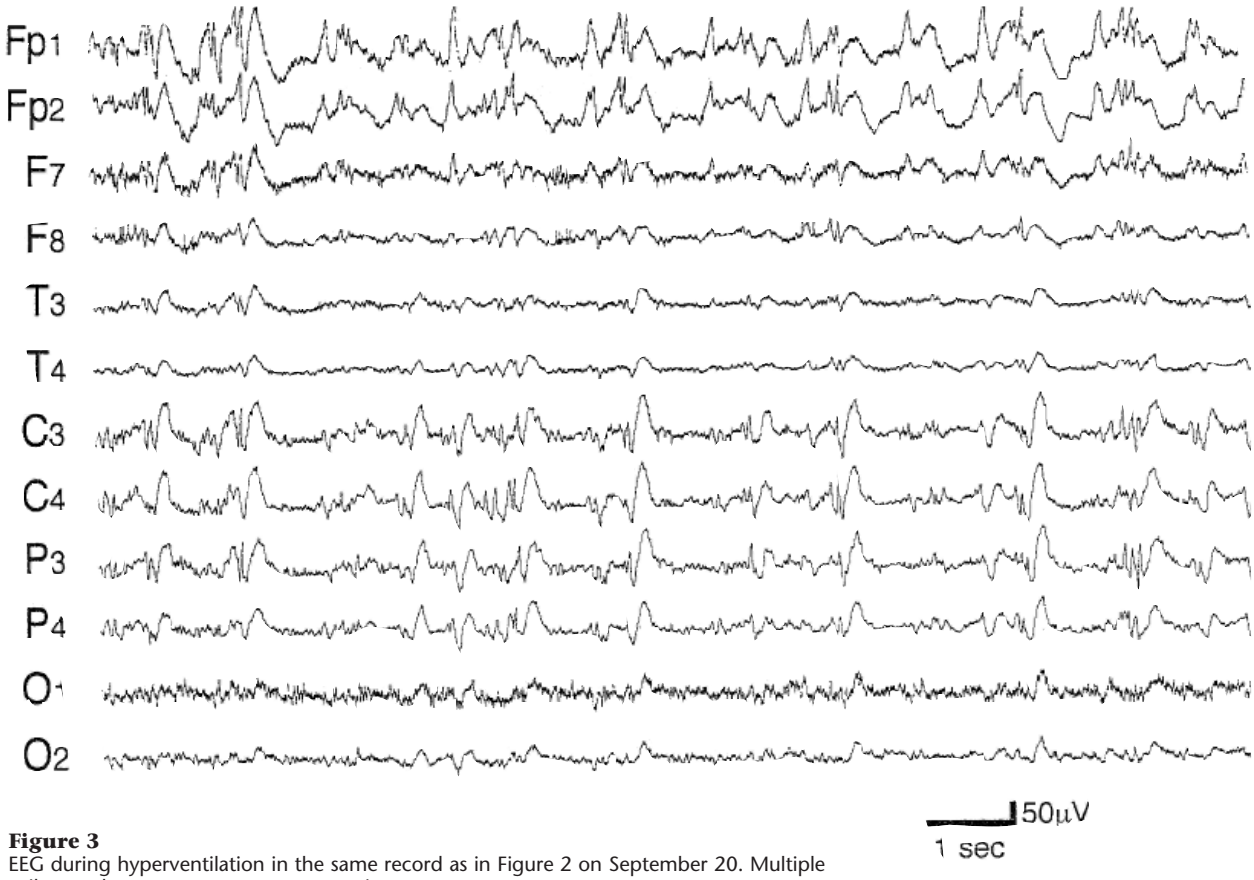

Figure 3
EEG during hyperventilation in the same record as in Figure 2 on September 20. Multiple spikes or sharp waves were more prominent.

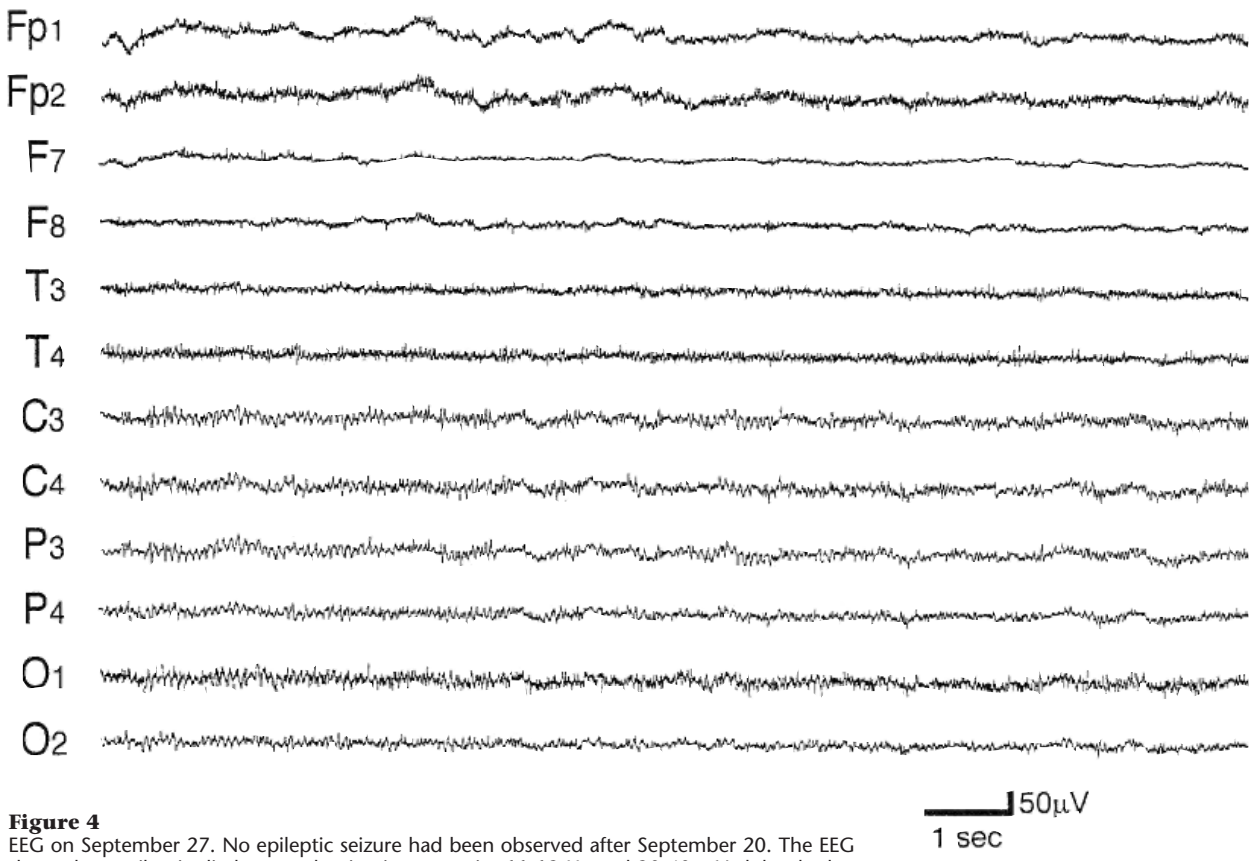

Figure 4
EEG on September 27. No epileptic seizure had been observed after September 20. The EEG showed no epileptic discharges, dominating posterior 11-13 Hz and 30-40 μV alpha rhythm recovering to within normal limits.

these effects (Schwab et al 1969; Snoey and Bessen 1990). Neuroleptic malignant syndrome was induced by the sudden cessation of amantadine (Bower 1994), with that of other Parkinsonian drugs (Toru 1981). Epileptic seizures have also been reported (Schwab et al 1969; Brown et al 1987; Gualtieri et al 1989; Douglas 1990), in spite of some influential reports that have claimed benefits from amantadine in the treatment of refractory epilepsy in childhood (Shields et al 1985; Shalev et al 1987; Shahar and Brand 1992).

Amantadine has been used as a treatment for some neuroleptic side effects, such as Parkinsonism and dystonia (Gualtieri et al 1989). In a schizophrenic patient, who had developed the Pisa syndrome (Ekbom et al 1972) following neuroleptic medication, amantadine was administered orally. No improvement was observed, but a generalised tonic-clonic convulsion occurred. We recorded serial EEGs, including EEGs before convulsion and after the cessation of amantadine. To our knowledge, this is the first report to show the EEG of a patient with an amantadine-induced convulsion.

Description of the patient, methods and results

A 63-year-old woman with a history of chronic schizophrenia, who satisfied the diagnostic criteria for schizophrenia of the Diagnostic and Statistical Manual of Mental Disease, 4th edition revised [DSM-IV] (American Psychiatric Association, 1994), developed the Pisa syndrome involving tonic flexion of the trunk to the left side accompanied by its slight rotation following neuroleptic medication (6 mg of haloperidol and 75 mg of chlorpromazine). Amantadine was commenced at a dose of 200 mg per day (100 mg twice daily) on September 4, but no improvement of the Pisa syndrome, or any adverse effect, was noticed. The dosage was increased to 300 mg per day (100 mg three times daily) on September 18, and two days later (on September 20) a generalised tonic-clonic convulsion occurred. There was no evidence of trauma and no previous history of seizure disorder. Laboratory evaluations, including a blood cell count, electrolytes, liver and renal panels, urinalysis, and an electrocardiogram, were all within normal limits. The CT brain scans on the same day did not show any abnormalities. Amantadine was gradually tapered and discontinued. Since then, no epileptic seizure has been observed.

Scalp electroencephalograms (EEGs) were recorded with a 14-channel electroencephalograph (Nihon Kohden Corp, Tokyo, Japan) using unipolar montages. The electrodes were placed at Fp1, Fp2, F7, F8, T3, T4, C3, C4, P3, P4, O1, and O2, according to the International 10-20 system. In the unipolar montages, all scalp electrodes were referenced to the ipsilateral earlobe. The time constant was 0.3 seconds, and the 50 mV calibration was amplified to be 5 mm on the recording.

The first EEG was recorded on September 11 (Fig. 1), 7 days after the administration of amantadine at a dose of 200 mg per day, when the patient was free of seizures. Posterior 11-12 Hz and 30-40 mV alpha rhythm was dominant and thought to be within normal limits.

The second EEG was conducted on September 20 (Fig. 2), 2 days after increasing the amantadine to a dose of 300 mg per day, when the generalised tonic-clonic convulsion occurred. It revealed multiple spikes or sharp waves with slow waves at Fp1, Fp2, C3, C4, P3, and P4, which were slightly larger over the left hemisphere. These multiple spikes or sharp waves were more prominent during hyperventilation (Fig. 3).

The EEG on September 27 (Fig. 4), when amantadine was gradually tapered and discontinued, showed no epileptic discharges, dominating posterior 11-13 Hz and 30-40 mV alpha rhythm recovering to within normal limits.

Discussion

Because the patient had not had any previous history of seizures and has been free of seizures since the cessation of the amantadine, it is clear that amantadine induced the generalised tonic-clonic convulsion. Normal EEGs before and after a convulsion and a normal CT brain scan support this.

Although amantadine was found to be effective as an adjunctive anticonvulsant agent in the treatment of children with refractory myoclonic or absence epilepsy (Shields et al 1985; Shalev et al 1987; Shahar Brand 1992), some tonic-clonic, tonic and atonic seizures of epileptic patients were exacerbated by amantadine (Shields et al 1985). The present finding suggests that amantadine may also have an epileptic effect.

The epileptic and antiepileptic mechanisms of amantadine have not been elucidated; however, they may be related to DA-agonist properties. It has been shown that amantadine releases DA from peripheral neuronal storage sites and delays the reuptake of DA by neural cells (Fletcher and Redfern 1970; Scatton et al 1970; Farnebo et al 1971; Von Voigtlander Moore 1971; Heimans et al 1972). Furthermore, there is additional information to suggest a direct stimulation of postsynaptic DA receptors (Bailey Stone 1975). Clinical observations indicate that neuroleptics, which block DA neurotransmission, markedly reduce the

threshold for seizures. Photically induced discharges in patients with generalised photosensitive epilepsy were transiently blocked by apomorphine, a direct DA-receptor agonist, while spontaneous spike-and-wave discharges in patients with nonphotosensitive primary corticoreticular epilepsy were not blocked (Quesney et al 1981).

There exist contradictory data concerning the participation of DA in electrically and chemically induced seizures in animals. L-Dopa potentiated pyrimethamine-induced seizure (Amabeoku Chikuni 1994). MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) pretreatment, which causes the depletion of striatal DA, attenuated the severity of the convulsion and the mortality induced by kainic acid (Bonuccelli et al 1994). The behavioural tonic and clonic seizures elicited by (+)3-PPP (3-(3-hydroxyphenyl)-N-(1-propyl)piperidine) were prevented by haloperidol and spiperone (Pieretti et al 1995). In contrast to these results, other studies indicate that central DArgic stimulation decreases the susceptibility of experimental animals to seizures. DA decreased the orthodromically evoked hippocampal population spike in rats (Kaneko et al 1993). L-Dopa potentiated the anticonvulsant action of both phenobarbital and diphenylhydantoin in the electroshock test, while amantadine decreased that of diphenylhydantoin (Kleinrok et al 1980). These results indicate that there may be a selective epileptic and/or antiepileptic mechanism in the DArgic system.

A growing body of recent studies suggests that there appear to be different actions between the D1 and D2 receptors (Starr 1996). D1 agonist SKF 38393 injected intraperitoneally into rats reduced the threshold to convulsions produced by systemically administered pilocarpine, whereas D1 antagonist SCH 23390 prevented seizure activity (Barone et al 1992). In addition, the pretreatment of the dorsal hippocampus with D2 agonist LY 171555 delayed the appearance and reduced the intensity of pilocarpine-induced convulsions, while raclopride, a selective D2 antagonist, dose-dependently facilitated motor seizures (Alam Starr 1993). This is compatible with the result that sulpiride, which is a potent dopamine receptor blocker specific for the D2-receptor, produced a marked reduction in the late afterhyperpolarization of pyramidal CA1-neurons in the hippocampal slice preparation (Dinan et al 1987). On the other hand, the stimulation of D1 receptors by SKF 38393 depressed the spontaneous activity of CA1 neurons in the hippocampal slices of the rats, whereas LY 127809, D2 agonist, increased the firing rate of the recorded neurons (Smialowski and Bijak 1987). SKF 38393 decreased the neuronal firing rate of hippocampal CA1 neurons in the model of low calcium spontaneous epileptiform discharges (Smialowski 1990). The bath application of SKF 38393 in hippocampal pyramidal cells produced a hyperpolarization of the resting membrane potential (r.m.p.) and an increase in the afterhyperpolarization (AHP) amplitude and duration, while the activation of D2 receptors through LY 171555 produced a depolarization of the r.m.p. and a depression of the AHP (Berretta et al 1990). Although the effects of DA receptor agonists and antagonists vary in different models of epilepsy, the works previously cited suggest that the two DA subtypes, D1 and D2, may exert opposing influence in controlling seizure activity. Attention must be paid to the fact that the DA affinity to D1 and D2 receptors is different and that the concentration of both receptors is not the same (Smialowski and Bijak 1987). It was found that the density of D1 receptors was greater than that of D2 receptors in many brain regions (Richfield et al 1989). These factors might be involved in the epileptic mechanisms of amantadine in this case.

Lastly, it should be noted that the incidence and severity of side effects markedly increase when the daily dose exceeds 200 mg per day. Patients with a history of epilepsy must be closely observed when taking this drug (Douglas 1990).

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