UNIVERSITY OF LONDON

THE ATTENTION DEFICIT OF SCHIZOPHRENIA

DISSERTATION SUBMITTED TO LONDON UNIVERSITY
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BY
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ABSTRACT

Attention is known to be impaired in schizophrenia but the reason remains unclear. A new auditory test was devised (PAT) that measures simultaneously selective attention, sustained attention and the rate of information processing. It was validated by a longitudinal (two year), double-blind, cross-over study of chlorpromazine (CPZ) versus placebo in 20 schizophrenic in-patients, who were tested fortnightly and compared to healthy subjects. The results showed that the essential attention deficit in schizophrenia is intermittent sustained attention. PAT errors increased significantly with placebo and responded to CPZ. The errors discriminated patients from healthy subjects; correlated with parallel clinical ratings; and measured the absolute severity of illness, since normal errors 'predicted' which patients were ready for hospital discharge. Current models of attention are inadequate to explain the PAT findings. Possible causes of the attention defect were examined. It was argued that attention is deployed by plans that are constantly challenged by rival options. Distraction causes a switch of plan when a rival option is adopted. However, increased distractibility does not explain schizophrenia. The defect lies in the selection and maintenance of plans. A new cognitive model was proposed whereby bottom-up 'meaning' and 'top-down' plans are selected by integration with the context. The model was provided with a neurological counterpart. Schizophrenia was presented as an organic psychosis with neuropathology affecting the cortico-thalamic basal ganglia circuit. Derangement of this anatomical circuit impairs working-memory and degrades context. Evidence was insufficient to support a primary integration failure, but degraded context would cause analogous defects. Defects of plan selection (integration with the context) and plan maintenance (working-memory) would disrupt attention. All three aspects of planning are deficient in schizophrenia. The model explained multiple behavioural and cognitive deficits produced by schizophrenia and other neurological conditions, and the PAT results.
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To ANNE

as a meagre consolation
and with love
PREFACE

The fact that few longitudinal studies have been reported in schizophrenia must be to a large extent because of the huge resources required. Many researchers may have been deterred for want of funds or for a lack of logistical support. The project reported here was primarily sponsored by The Wellcome Foundation Ltd (Dr Thomas Hanley) which gave the Author a fellowship with generous financial support for four years. Negotiations conducted by Dr Bernard Adams (University College Hospital and Friern Hospital) resulted in a further donation from The Friern Hospital Management Committee. This permitted the conversion of a villa in the grounds of Friern Hospital to house the self-contained Neuropsychology Research Unit. The later phase of the Unit was funded by The Sir Jules Thorn Medical Research Endowment Trust. Professor Desmond Laurence (University College Hospital Medical School) frequently mediated with the Trust.

Many individuals devoted considerable effort to make the project a success. These include the nursing staff of the villa notably charge nurses Ann Davies and Joe O'Leary, but also their colleagues Mr Pardoe, Mr McGranaghan and others, all of whom watched over the patients with great care and understanding. The patients' contentment and well-being were absolutely critical. Even more fundamental was the willingness of so many patients to volunteer and collaborate for such a long period in a demanding schedule of testing. I am endebted to them.

Others at Friern Hospital who were outstanding in their support included the hospital chairman Mrs Peggy Jay, the heads of nursing, and many members of the Works and Maintanance Department.

In addition I wish to thank the following for their invaluable contributions: Professor Neville Moray (Sheffield University) for suggesting a study of auditory attention and dichotic testing; Drs Bernard Adams, Peter Fleming and Alan Gardiner for painstaking clinical ratings; Drs Hugh Norris and Saniha Zaki for hours of assistance with the test schedule; Mr Barry Graham (Medical Unit, University College Hospital Medical School, London) for considerable technical support; Dr Laurence Freedman (MRC Statistical Unit) for advice concerning the error index; Mrs Jan Voerman and Mrs Steve Stulemeier (Statistical Group, Medical Unit, Organon International BV, Oss) for help with the statistical analysis of the Chapter II data;
Dr John Gilbert (Royal Northern Polytechnic) for the loan of four-track recording equipment; Mr E. Dymock (Glaxo Laboratories Ltd) for a donation of the drug and placebo supply; Mr P. Williams (Pharmacy Department, University College Hospital, London) for organizing the drug packaging and double-blind coding; Mrs Susan Collings for her precision and patience when speaking lists of digits; Duster Morgan for helping to discover the algorithm; and both Amanda Robins and Matthew Partridge for help with scoring the data for successive subtest thirds.

In more recent years Professor Sandra File (Psychopharmacology Research Unit, Guy's Hospital, UMDS, London) encouraged me to reopen boxes of data which had twice travelled to and from the Continent, and then urged me to publish and submit this thesis. Her exhortations persisted and she has added her unremitting support, kindness and valued critical comment. At the same time new technology has meant that the methodology used by the project can be made more accessible. Two former colleagues Dr Henk van Riezen (Ciba-Geigy, Basle) and Dr Geoffrey Dunbar (SmithKline Beecham) encouraged me to find a manufacturer for the attention task and helped me in the search. As a result Dr Lothar Ludwig (Zak GmbH) undertook the manufacture and invested considerably in the method. It was he who suggested that the instrument should be named the PAT (Pigache Attention Task). The prospect that the test would become available and put to use was highly stimulating and has materialized.
## GLOSSARY & ABBREVIATIONS

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<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
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<td>CPT</td>
<td>Continuous Performance Test</td>
</tr>
<tr>
<td>CPZ</td>
<td>chlorpromazine</td>
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<td>CT</td>
<td>computerized tomography</td>
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<tr>
<td>Diotic</td>
<td>a single stimulus delivered to both ears</td>
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<tr>
<td>Dichotic</td>
<td>a different stimulus to each ear, simultaneously</td>
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<td>F1</td>
<td>Fast diotic subtest</td>
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<td>F2</td>
<td>Fast dichotic subtest</td>
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<tr>
<td>$I_E$</td>
<td>Index of Errors</td>
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<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
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<td>LTS</td>
<td>Long-term storage</td>
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<tr>
<td>$M/I_E$</td>
<td>Mean Index of Errors</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>n</td>
<td>number</td>
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<tr>
<td>PAT</td>
<td>Pigache Attention Task</td>
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<td>PET</td>
<td>positron emission tomography</td>
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<td>rCBF</td>
<td>regional cortical blood flow</td>
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<td>RL</td>
<td>Response latency</td>
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<td>RT</td>
<td>Reaction time</td>
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<td>Standard deviation</td>
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<td>Standard error of the mean</td>
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<td>S2</td>
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<td>WCST</td>
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CHAPTER I
Introduction to the Thesis

It is generally recognized that attention is defective in schizophrenia. Bleuler (1911: translation 1950) included an impairment of attention amongst the symptoms of schizophrenia assembled in his now classical description. Kraepelin (1913: translation 1919) related the defect specifically to directed and sustained attention. Since then numerous experimental reports have confirmed the pervasiveness of attentional disturbances in schizophrenia.

Attention is often described as multifaceted thereby including sustained attention, concentration, focussed attention, selective attention, divided attention (switching of attention), span of attention (broad/narrow), orientation, active attention (voluntary), and passive attention (involuntary). In the Author's view this list, which is probably not exhaustive, denotes a dazzling number of facets. A new perspective is needed to organize these aspects of attention into the various operations of a more basic functional apparatus.

Many aspects of attention appear to be deficient in schizophrenia. For example, Venables (1964) suggested that an abnormal broadening or narrowing of attention characterizes acute and chronic schizophrenics, respectively; McGhie and Chapman (1961) and Payne (1961) proposed a defect of selective attention; Yates (1966) countered that an abnormal slowness impairs the information processing of schizophrenics, thus challenging attentional hypotheses; and Kornetsky and Mirsky (1966) proposed a defect of sustained attention secondary to hyperarousal. Holzman, Levy and Proctor (1978) added to these hypotheses a disorder of involuntary attention. On this basis, should one envisage multiple lesions of attention or a single lesion viewed from multiple facets? Is impaired attention the cause of schizophrenia or is it secondary to a more fundamental cognitive dysfunction?

The role of attention is also critical to the implementation of numerous cognitive processes, e.g., the range of controlled processes described by Schneider and Shiffrin (1977) and Shiffrin and Schneider (1977). The present investigation of disordered attention in schizophrenia offered an opportunity to examine relationships between specific modes of attention. Also, by monitoring the effects and limitations of a standard neuroleptic upon these modes of attention, it opened the enquiry to a
broader field of cognitive theory. The promise was an understanding of neuropsychological processes relevant to models of normal cognition and of schizophrenia. It was hoped that this would indicate how schizophrenics might deviate from normal and thereby stimulate new approaches to therapy.

1 ATTENTIONAL THEORIES OF SCHIZOPHRENIA

The studies of this thesis tested the hypotheses of a selective attention defect (McGhie and Chapman, 1961; Payne, 1961), of abnormal slowness (Yates, 1966), and of a sustained attention defect (Kornetsky and Mirsky, 1966), simultaneously in chronic schizophrenia. The theories are sometimes described in different terms, but they remain as relevant today as when they were first proposed (e.g., Spohn and Strauss, 1989; Grillon et al., 1990; Healy, 1990; King, 1990; Granholm, Asarnow and Marder, 1991).

1.1 Selective Attention

Schizophrenic thought disorder was attributed to impaired selective attention by McGhie and Chapman (1961) and Payne (1961). The failure of a filter (Broadbent, 1958) would allow irrelevant information to enter a limited capacity, short-term memory buffer and to bump out information already there. The result would be a flood of distracting sensory input and a breakdown of normal cognitive function (Grimes and McGhie, 1973). This theory with varying emphasis put on the external and possible internal sources of distraction has been supported by many authors (Taylor and Hirt, 1975; Schneider, 1976; Oltmanns, 1978; Grillon et al., 1990). A selective attention deficit may be measured directly by identifying the intrusion of distractors into the response, or indirectly from an impairment of performance when distraction is introduced.

Schizophrenics were more impaired than healthy subjects by the addition of distraction when performing a variety of tests (Chapman and McGhie, 1962; McGhie, Chapman and Lawson, 1965; Grimes and McGhie, 1973; Schneider, 1976; Oltmanns, Ohayon and Neale, 1978), and they improved with neuroleptic drugs (Grimes and McGhie, 1973; Maloney et al., 1976).
1.2 Information Processing Rate

Observations by Babcock (1930 & 1933) led her to suggest that slow mental processing might be the primary deficit in schizophrenia. This hypothesis was developed by Yates (1966) who proposed that "the primary deficit in schizophrenia consists in the abnormally slow rate at which information in the primary channel is processed". As a consequence new information replaces that already in short term storage before the latter is fully processed. Yates supposed that under time-pressure the information loss would lead to various forms of thought disorder: fragmented speech, derailment, and loose associations. The hypothesis was originally proposed as an alternative to the attentional model of McGhie and Chapman (1961). However, slowness could also result from a failure of attention which normally accelerates information processing (Posner, 1980).

The rate of information processing can be measured directly as the decision time (excluding the response time) taken to perform accurately a task that involves no memory search. It may be estimated, too, by varying the stimulus rate and measuring performance accuracy.

Slow central processing by schizophrenics relative to control subjects has been demonstrated with a variety of procedures. This slowness was shown in comparisons with healthy subjects (Shapiro & Nelson, 1955; Yates & Korboot, 1970; Korboot & Yates, 1973; Korboot and Damiani, 1976; Russell and Page, 1976; Wijsinghe, 1977) and patients with other psychiatric conditions (Korboot and Yates, 1973; Marshall, 1973; Wishner and Wahl, 1974; Wijsinghe, 1977; Davidson and Neale, 1974; Hemsley, 1976; Hemsley and Zawada, 1976; Braff and Saccuzzo, 1982; Saccuzzo, Braff and Sprock, 1982). Also, slow reaction times are generally observed (reviews: Nuechterlein, 1977; Mannuzza, 1980; Rist and Cohen, 1991). The literature is not very positive, however, about the possibility of reversing this slowness with neuroleptic drugs.

1.3 Sustained Attention

Kornetsky and Mirsky (1966) and Mirsky (1969) noted that chronic schizophrenics made excessive errors on the Continuous Performance Test (CPT) and interpreted this as impaired sustained attention. For them, the impairment was
secondary to a malfunction of the reticular activating system, causing a core deficit of hyperarousal in some chronic schizophrenic patients. The notion of hyperarousal stemmed from the beneficial effects of neuroleptics on CPT performance and from animal studies. A well known failure of sustained attention is the decrement of performance with time on a task. This was first demonstrated for the CPT by Nuechterlein, Parasuraman and Jiang (1983) in healthy subjects. A very small but significant decrement from baseline of a measure equivalent to the percentage of targets detected was found with highly degraded visual targets, but only after five minutes of performance. This effect was not replicated with schizophrenics (Nuechterlein et al, 1986). However, Nestor et al. (1990) did succeed in finding a small temporal decrement of CPT performance in both schizophrenic and healthy subjects when degraded visual stimuli were presented. This was significantly greater for the schizophrenics, but only after seven minutes on the task. The typical duration of the CPT is five minutes.

Rappaport et al (1972a, b) suggested, on the basis of a rather dubious study, that schizophrenia might result from the intermittent focussing and defocussing of attention. An intermittent failure of sustained attention might be expected to operate randomly throughout tasks requiring vigilance. Hence an intermittent attention hypothesis would account, too, for the many reports of poor CPT performance by schizophrenics with non-degraded stimuli. Also, the errors of schizophrenics increased when distraction was added (Walker, 1981; Mussgay and Hertwig, 1990).

2. GENERAL OBJECTIVES

The studies reported in this thesis were designed to serve practical and theoretical purposes. The practical considerations will be presented first because they underline the clinical relevance of studying attention in schizophrenia (Study 1: Chapters IV and V; Study 2: Chapter 6; Study 3: Chapter VII). The more theoretical aspects are presented subsequently (Study 4: Chapter VIII; Study 1: Chapter IX). Finally, a new theory of schizophrenia is proposed (Chapter X).

3. PRACTICAL UTILITY

Forty years have elapsed since chlorpromazine (CPZ) was first used to treat schizophrenia (Delay and Deniker, 1952) yet the use of neuroleptics still poses problems. We are still uncertain as to which patients would do well without neuroleptics, which drug to prescribe for a given patient, how much to give, and for how long to treat. These uncertainties matter because current drugs can be seriously toxic after short and prolonged uses. A part of the problem lies in our inadequate methods for measuring the clinical response, whether it be spontaneous or the result of therapy. At present, observer rating scales (subjective) provide the only valid methods for quantifying symptoms and the severity of illness in schizophrenia. It is nonetheless rare for such scales to be used in everyday patient care. A need exists for objective measures that are also valid, reliable, and suited to repeated application, to monitor the course of schizophrenia (Tsuang, 1982). For routine use, they should be applicable by non-medical staff.

Psychometric tests offer the most obvious alternative to rating scales, at least until more specific neurological or biochemical indices are found. Cognitive tests including measures of attention were the subject of several recent reviews concerned with their sensitivity to neuroleptic drugs (Heaton and Crowley, 1981; Medalia, Gold and Merriam, 1988; Spohn and Strauss, 1989; Cassens et al., 1990; King, 1990). Most reviewers have commented upon the generally poor quality of research in this field, with respect to insufficient drug 'washout', dosage and duration, too little use of placebo, a lack of double-blind procedures, inadequate statistical methods and power, and the absence of concomitant clinical ratings. This limited the evaluation of many methods. However, a few of the tests were promising but required further validation.
Cassens et al. (1990) noted that, so far, the results of objective tests in schizophrenia have led some to dismiss them as the barren province of researchers and without value for practising psychiatrists. The general consensus was that the Continuous Performance Test of Rosvold et al. (1956) is by far the most validated procedure, but it is also unreliable (probably due to its methodology). The CPT is believed to measure sustained attention (Mirsky and Kornetsky, 1964). Hence from a practical standpoint this aspect of attention is a vein to be quarried.

4 METHODOLOGICAL CONTRIBUTION

Certain aspects of the studies described in this thesis represent methodological innovations (auditory attention task, error index, and an algorithm). Also the design was unusual (longitudinal, with double-blind administration of chlorpromazine or placebo, cross-over of the treatments, and a long duration of placebo), though not an innovation. All these features are commented upon in the sections that follow.

4.1 PAT

This thesis (Chapter II) describes a new attention task to assess schizophrenia (referred to as the PAT\(^1\)). The PAT is an auditory attention task chosen because this modality in schizophrenia is particularly vulnerable to hallucinations. Moreover the PAT stimuli are heard over headphones which ensures they are encoded. The PAT subtests provide different stimulus rates plus diotic/dichotic modes of delivery. The diotic mode comprised one digit string to both ears; the dichotic mode comprised a different digit string to each ear, synchronously. As a consequence the PAT measures simultaneously: sustained attention, information processing capacity (rate effects and response latencies), and selective attention. It imposes no memory load.

4.2 PAT Error Index

The error index \(I_E\) was proposed by Pigache (1976) for reasons that were fully discussed earlier. There it was argued that signal detection theory might not apply to suprathreshold stimuli, to healthy subjects making very few errors, and to patient

\(^1\) Adopted from the acronym of a solid-state instrument PAT ® (Pigache Attention Task).
groups. Rival indices were shown to be unsatisfactory. The error index $I_E$ reflects the *reciprocity* of 'go' and 'no-go' response strategies as determinants of commission and omission errors, respectively. The index sums omission and commission errors then augments the omission error score (the most frequent type of error) by a correction for random response tendencies (operant/'go'), as indicated by the prevailing commission error rate. The use of one response variable $I_E$ for a single subtest and the one variable $M_{I_E}$ (mean $I_E$) for all four subtests simplifies analysis and data presentation.

4.3 General Study Design

An important practical question is how long does it take for a schizophrenic to be pharmacodynamically 'free of drug' after neuroleptic withdrawal? The answer requires a longitudinal study since it probably depends upon which variable (behavioural or physiological) is studied. Three years after the present project had begun Spohn (1973) advocated a very similar approach: "I propose that the time-course of effects of anti-psychotic drugs upon selected psychological processes in which psychological deficit or dysfunction has been demonstrated or suspected be studied in schizophrenics in parallel with the assessment of the time-course of effects upon symptoms and morbidity". Since then no such longitudinal study has been reported. However, one recent extensive study performed ratings every two months during two years for a life-table analysis of relapse rates (Heresco-Levy et al., 1993). Otherwise, the few longitudinal studies published generally assessed patients twice, before and after an interval of one year or more.

It is perhaps surprising that so little intensive longitudinal research has been performed given that more than fifty percent of schizophrenics develop a chronic illness. Tsuang (1982) observed "It cannot be overemphasized that future follow-up studies of schizophrenia should include both longitudinal clinical course and outcome of the patients to obtain a comprehensive picture of schizophrenia". However, many factors discourage such studies. They are costly, difficult to conduct, statistically problematic, and require the cooperation of patients who are particularly liable to default (especially when outpatients).
In order to test the clinical relevance of the PAT (validity and reliability) it was given fortnightly to chronic schizophrenics for one year during Study 1 and likewise for a second year during Study 2.

4.4 Placebo

Spohn and Strauss (1989) recently reviewed well over 400 reports on the influence of neuroleptics on schizophrenia published since 1955; they cited the first report (abstract) of the present findings (Pigache and Norris, 1973a) amongst only sixteen behavioural studies which met stated criteria of rigour. Hence this full report of the PAT data obtained in that study appeared still very relevant, especially since Spohn and Strauss observed "that it is logistically and practically more difficult to perform the kind of studies we have reviewed here than it was 15 years ago." (p. 377).

Schizophrenia research is hampered today by the general use of neuroleptic drugs. Sometimes schizophrenics may be found who are drug-free and suitable as volunteers for short-term research projects. Patients who default in taking drugs, or refuse them, comprise a self-selected and idiosyncratic group. Those who can be controlled without drugs are also atypical. Thus it still remains necessary from a research perspective to assign patients randomly to drug-withdrawal, which is no longer easily justified. Even so, selection will not be free of bias (Spohn, 1980). For example, it would be difficult to justify withdrawing drugs from patients who relapsed after previous attempts (Gardos and Cole, 1978).

The justification for a trial of placebo (in the early nineteen-seventies) was the perceived need to check, periodically, that the patients continued to require neuroleptics given that these drugs produce manifold side-effects. Although the proportion of patients who relapse when drugs are withdrawn has varied between studies it is evident that many schizophrenics maintained on long-term neuroleptics, do not always require them (Priem and Klett, 1972; Davis, 1975; Gardos and Cole, 1976 and 1978; Hogarty and Ulrich, 1977; Wistedt, 1981). The variation between studies is due at least partially to differences of relapse criteria (Falloon et al., 1983). Drug withdrawal benefits patients who no longer need drugs. Unfortunately it entails a relapse for those who do. Nonetheless, a policy of attempting to withdraw drugs every two to four years (Johnson, 1979; Klein et al., 1980), or every five years...
(Johnson, 1990), has been proposed. This important clinical decision would be better based if a placebo were substituted for the neuroleptic drugs, instead of stopping the medication overtly, especially if those assessing the patients are made 'blind' to the treatment change.

4.5 An Algorithm to Classify Trends

One manifestation of impaired sustained attention is the well known performance decrement that worsens with time on a task. A demonstration of this effect with the PAT would confirm that it measures sustained attention. Under optimal conditions this would be evident as a trend of increasing errors with time. Data subjected to a trend analysis are usually averaged at each observation point. Consequently, the range of individual profiles is minimized by the average and all other detail is hidden between the confidence limits. The lost detail, however, may be interesting and potentially pertinent to the interpretation. For example the expected trend might be obscured by intermittent lapses of attention, or by errors occurring at the start of a subtest before attention is fully engaged. Thus a procedure is needed which would restore the detail sufficiently to reveal any relevant component trends.

An alternative mode of analysis would be to apply parametric or non-parametric methods to test for higher-order trends, thus reducing the residual variance. These procedures, however, require many observations, the results may be difficult to interpret, and the conclusions can invite dispute.

Accordingly a novel algorithm was devised (Chapter III) which would classify the major trends relating to three sets of observations, e.g., the successive one-thirds of a task. The algorithm was used to identify performance differences between healthy subjects and schizophrenics (Chapter VIII) and to determine if sustained attention varies with increases in the severity of schizophrenia (Chapter IX).

5 OBJECTIVES OF SPECIFIC STUDIES (PRACTICAL)

5.1 Study 1: Validation of the PAT

Study 1 sought to test the clinical relevance of the PAT (validity and reliability). Accordingly the PAT was given fortnightly to chronic schizophrenics for one year during which ten weeks of placebo were substituted (double-blind) for
chlorpromazine. Since CPZ is an effective antipsychotic drug, true changes of the illness would be expected to follow the changes of treatment, unless the patients no longer required their drug. The patients were also rated clinically and monitored physiologically (not reported here). It was further expected that the ratings would correlate with the PAT. All relevant measures of change should also 'predict' hospital discharge (an index of substantial recovery). The main statistical analysis is reported in Chapter IV. However statistical analyses are not well suited to the comparison of parallel longitudinal changes (PAT and rating scale data). Accordingly these temporal relationships are also presented graphically in Chapter V.

5.2. Study 2: Neuroleptic Dose Escalation

Study 2 applied the PAT in answer to an important clinical question: "When should the dose of neuroleptic be increased in the treatment of schizophrenia?". Gardos and Cole (1978) and Ayd (1975) concluded from their reviews of the literature that high doses of neuroleptics often benefit treatment resistant schizophrenics, and schizophrenics under 40 years, who have been hospitalized for less than 10 years. Later, Klein et al. (1980) reviewed five double-blind studies in chronic schizophrenia where 'very high' doses of chlorpromazine (CPZ) were compared to 'standard' doses, and four similar studies of fluphenazine. They concluded that "megadoses should still be considered for patients chronically refractory to standard treatment", but added that the value of megadoses in long-term chronic patients remains problematic, in terms of worthwhile benefits relative to the risk of tardive dyskinesia. More recently Baldessarini, Cohen and Teicher (1988) conducted an extensive review and showed that moderate doses of neuroleptics are generally adequate, and unusually high doses of no demonstrable benefit, in the majority of cases. High doses (oral) have been regarded as 2.0 g CPZ per day (Prien and Cole, 1968), 15 mg haloperidol per day (Hollister and Kim, 1982), 40 mg thiothixine per day (Kim and Hollister, 1984), and neuroleptics generally at doses equivalent to approximately 600 mg CPZ, or more, per day (Baldessarini et al., 1988). Brotman and McCormick (1990) still argue the case for a limited trial of neuroleptics at doses greater than 15 mg haloperidol per day in treatment resistant schizophrenics (comprising 12.5% of their community mental health practice). A recent review of pharmacokinetic studies of neuroleptics in schizophrenia
(Verghese, Kessel and Simpson, 1991) concluded that the blockade of dopamine-2 (D2) receptors is virtually complete after 10 mg haloperidol and that non-response involves different mechanisms.

An abiding problem is how to estimate the correct neuroleptic dose for a particular patient? Dose titration remains the most generally recommended method (eg. Pi and Simpson, 1981; Johnson, 1990), but it can be a difficult policy to follow without a clear end-point. The studies cited by the preceding reviews relied upon ratings to determine the clinical response. Such methods are subjective and not too accurate. Measurement of the D2 receptor blockade estimates the relevant drug effect, but not the residual severity of illness. In this situation the PAT offered an objective means to monitor the clinical response as the neuroleptic dose was increased during a second consecutive year for ten of the original patients. The results are reported in Chapter VI.

5.3 Study 3: A Comparison of the PAT and CPT

The measurement of sustained attention appears to provide an objective index of the intensity of schizophrenic illness. Two tests exist which serve this purpose, the PAT and the Continuous Performance Test (CPT) of Rosvold et al. (1956). Both appear to be reliable and repeatable and so well suited to monitoring the course of schizophrenia. Although the term CPT has now become generic, embracing many versions of the original standard, it usually denotes an unbroken presentation of differing stimuli for several minutes, with some designated as targets for a response. The term CPT is thereby similar to tasks known otherwise as successive go/no-go discriminations.

Numerous studies with different versions of the visual CPT have shown that this procedure discriminates between schizophrenics and healthy subjects or patients with other psychiatric conditions (Section 1.3, above). Moreover statistically significant relationships were obtained between CPT omission errors and concomitant clinical ratings of schizophrenia (Orzack, Kornetsky and Freeman, 1967; Spohn et al., 1977). Consequently the CPT can be considered a valid measure of the psychological dysfunction found in schizophrenia. It is now established as benchmark procedure.
Auditory versions of the CPT exist and were compared to their visual counterparts (Williams, Lubin and Goodnow, 1959; Mirsky and Cardon, 1962; Sykes, Douglas and Morgenstern, 1972; Mussgay and Hertwig, 1990). In all studies both modalities of the CPT significantly supported the planned comparisons which comprised the effects of sleep deprivation upon healthy subjects (Williams, Lubin and Goodnow, 1959; Mirsky and Cardon, 1962), of chlorpromazine administration to healthy subjects (Mirsky and Cardon, 1962), of methylphenidate to treat hyperactive children (Sykes et al., 1972), and a discrimination of schizophrenics from healthy subjects and from alcoholics (Mussgay and Hertwig, 1990). Mirsky and van Buren (1965) examined centrencephalic epilepsy with both modalities of the CPT but report no comparison.

Two of the foregoing studies found no difference of performance between the two modalities (Williams, Lubin and Goodnow, 1959; Mirsky and Cardon, 1962). However, adventitious clicks from the apparatus accompanied the visual targets. By contrast, hyperactive children exhibited a significantly greater impairment with the auditory CPT than the visual CPT which was unaltered by methylphenidate (Sykes et al., 1972). A similar result was obtained with schizophrenics; whereas with healthy subjects and alcoholics the auditory and visual versions of the CPT produced similar errors (Mussgay and Hertwig, 1990).

A comparison of the PAT and an auditory version of the CPT was needed to assess their relative sensitivities in the measurement of schizophrenia. In addition a possible effect of order due to the fixed sequence in administering the PAT subtests was examined. The results are reported in Chapter VII.

6 THEORETICAL CONSIDERATIONS

The theoretical concerns of this thesis were adequately described in the preamble to this chapter and in Section 1. The contributions of selective attention, fast processing demands, and sustained attention to the PAT performance of schizophrenics were determined by comparison with healthy subjects (Chapter VIII: Study 4) and in relation to increasing severity of the illness (Chapter IX: an extended analysis of Study 1 data).
7 OBJECTIVES OF SPECIFIC STUDIES (THEORETICAL)

7.1 Study 4: A Comparison of Healthy and Schizophrenic Subjects

A necessary step was to show that the PAT discriminated between schizophrenics and healthy subjects when the patients were treated (CPZ) and untreated (placebo). Because the PAT tests three theories of schizophrenia simultaneously, the comparison with healthy subjects was broad and relevant. Thus Study 4 (Chapter VIII) asked if the PAT subtest affected healthy subjects and schizophrenics differently according to its requirements for: selective attention (variable: total dichotic errors), fast information processing (variable: total fast errors), and sustained attention (variable: error patterns across subtest one-thirds, as classified by the algorithm of Chapter III).

7.2 Study 1: What Does the PAT Measure in Schizophrenia?

The PAT variables particularly relevant to schizophrenia were expected to deteriorate most as the severity of illness increased. Thus the PAT data of Study 1 (Chapter IX) were further analysed to evaluate the contributions of: selective attention (variables: dichotic intrusion and total dichotic errors), fast information processing (variables: response latencies and total fast errors) and sustained attention (variable: error patterns across subtest one-thirds, as classified by the algorithm of Chapter III). Because the scale of Study 1 was far greater than Study 4 a vast quantity of data was generated. This permitted an extensive analysis of the interplay between the effects of distraction and presentation rate with respect to sustained attention. The relationship of these elements provides scope for interesting theoretical speculations.

7.3 A Neurological Model of Cognition and Schizophrenia

In the Author's view current models of attention are inadequate to explain the PAT findings in schizophrenia. A more comprehensive model is needed. Such a theory is proposed in Chapter X and will not be anticipated here. It may be stated, however, that in order to restrict the number of assumptions required and to keep them plausible an existing cognitive model was pressed into service, chosen for its explanatory power and supporting evidence. Modifications were nonetheless necessary which were not to appear *ad hoc* and arbitrary. Accordingly, constraints were sought
that would extend the model and increase its interest. It seemed logical that the limitations should be those an hypothesized neurological counterpart to the cognitive model itself. The first aim therefore was to produce a neurological model of normal cognition. Then this was tested by its ability to explain the known deficits produced by neurological lesions. Much evidence has accumulated to suggest that schizophrenia is not a functional psychoses but should be reclassified as an organic psychosis. Hence the model was applied to the neuropathology of schizophrenia and so united a large mass of clinical and research findings, including the PAT results.
CHAPTER II

Methods

1 GENERAL PROCEDURES

The procedures described in the section below were common to all four studies conducted.

1.1 Ethical Approval

All studies were approved by the Medical Committee of Friern Hospital. It may be noted that a referral to an ethical committee was unusual at the time (early nineteen-seventies) and was not generally obligatory. The patients were informed that they were free to withdraw from the study at any time and that the objective was to find out how much drug they needed, and if they needed drug at all. A zero dose-level could be inferred from this, but the patients were not told explicitly that placebo would be substituted for chlorpromazine.

1.2 Physical and Social Environments

The Neuropsychology Research Unit was purpose-built in a villa of Friern Hospital. It comprised accommodation for the 20 patients and a laboratory suite. Testing took place in a large sound-attenuated chamber equipped with an 'inter-com' and a one-way mirror. Ventilation produced a constant low level noise. The recorded temperature and humidity varied little. Patients sat alone when tested unless their behaviour was very disturbed. They understood that they could let themselves out of the chamber at any time. They never entered the experimenters' room.

The Nursing Administrators provided permanent senior nurses for the day-shift, but varying night staff. A friendly, informal, atmosphere was created while patients were under constant observation (except for rare weekends at home). Occupational and industrial therapy programs continued as before transfer to the Unit, and as requested. There was no rehabilitation pressure or 'threat' of discharge.
METHODS

(1) RECORDER I (TEAC)

Test Material

Signal A:

Signal B:

Signal C: (0) (7) (2)

Signal D: (3) (6) (0)

Tape-head

(4 forward tracks)

(2) RECORDER II (AKAI)

Test Instructions

Signal E: Spoken instructions

(3) PATCH-BOX: PHONO-JACKS

Signal E

Signal C

Signal D

(Diotic)

Mono

Stereo

(Dichotic)

Monitor

Patient

(4) 8-CHANNEL POLYGRAPH (SAN-EI)

Signals A+B

Response

Button-press

Figure II.1 Configuration of the PAT.
METHODS

2

THE PAT

All test-occasions began with the attention task (PAT). The equipment comprised a TEAC FM/AM tape recorder with four forward channels, an AKAI stereophonic tape recorder, a bank of eight SAN-EI preamplifiers, a SAN-EI eight-channel pen-writing polygraph, stereophonic headphones, a button-press switch, and connecting leads. The configuration of this equipment is shown in Figure II.1.

The PAT comprised four subtests constructed as follows. Tape recordings were made of a female elocutionist speaking strings of digits (0-9) for five minutes per subtest. The recordist heard metronome pulses which paced her speech; this step required the four channel TEAC. The digits were read either slowly, one every two seconds (event rate 0.5/sec); or fast, or two every second (event rate 2/sec); and were presented either diotically or dichotically. Thus four subtests were produced: slow diotic (S1), fast diotic (F1), slow dichotic (S2) and fast dichotic (F2). Next, a master tape was made by splicing together the short 'takes' and editing out the voice-pitch changes at the ends of each breath. Lastly, the entire sequence was rerecorded and the metronome pulses realigned to coincide with the onset of the digits. Stimulus durations were not determined, but the digits were short and sounded natural at each rate of delivery.

A five minute string of digits included 50 target 'noughts' spaced pseudorandomly. This resulted in average relative target rates of 33.3% and 8.3% for the slow and fast subtests, respectively. At both event rates (under diotic and dichotic presentation) no more than three targets occurred in succession, but at the fast event rate another digit always intervened between 'consecutive' noughts. The recordist was not told that 'nought' would be a target and so spoke the digits without emphasis.

The subject listened through headphones to recordings of a male voice giving instructions (AKAI recorder) followed by the female voice speaking the strings of digits (TEAC recorder). The four subtests were given in the order: slow diotic (S1), fast diotic (F1), slow dichotic (S2) and fast dichotic (F2), with a 10 minute rest between the diotic and dichotic subtests. Two different versions of the subtests were alternated between test-occasions. The relevant ear for the dichotic subtests was alternated both within and between test-occasions. The messages/signals delivered to the patients were continuously monitored.
Prior to the Study 1 ear wax was removed and hearing was tested by an audiometrician. Familiarization with the PAT procedures was provided by a practice tape which delivered two minutes of each subtest. Two runs were generally sufficient. At all times any asymmetrical hearing loss was corrected by a stereo-balance adjustment (used on all test-occasions) and the volume was adjusted as required. The patient held a button-press switch in his right hand and listened to the following instructions recorded by a male:

(a) At the beginning of each session:

"NOW YOU WILL HEAR SOME NUMBERS. PLEASE LISTEN CAREFULLY TO ALL THE INSTRUCTIONS AND TRY TO DO WHAT IS ASKED."

(b) Before the diotic subtests:

"NOW I WANT YOU TO PRESS THE BUTTON EVERY TIME YOU HEAR 'NOUGHT'. PRESS THE BUTTON FOR NOUGHTS ONLY."

(c) Before the dichotic subtests:

"NOW YOU WILL HEAR DIFFERENT NUMBERS IN YOUR TWO EARS. I WANT YOU TO LISTEN TO YOUR RIGHT EAR ONLY" (or left ear, as appropriate). Then, in the designated ear: "THIS IS YOUR RIGHT (or LEFT) EAR. I SHALL SAY 'NOUGHT'. PLEASE PRESS THE BUTTON EVERY TIME YOU HEAR 'NOUGHT' IN THIS EAR."

A recorded "THANK YOU" ended each subtest. The instructions were repeated until the patient performed as required. The patient was assured that "No one performs the test perfectly" and afterwards was always told "That was fine".

The polygraph permitted hand-scoring of errors and response latencies. It displayed the prerecorded metronome signals coincident with the digits (accuracy ± 0.03 sec) and opposing pen deflections which indicated 'noughts' delivered to the different ears. Another pen displayed the responses.

The scoring criteria sought to express how well the patients performed, i.e., too short a response interval after a target (for a response to count as 'correct') would artificially increase both omission and commission errors. Hence a 4 sec window (from the onset of a metronome mark for 'nought') was allowed for 'correct' responses at the slow event rate, and a 1.5 sec window at the fast rate. Multiple responses were rare, but possible in the interval between two digits at the slow event
rate. These were scored as one response, except when a late 'hit' was followed by a second 'hit'.

The measure comprised errors: missed noughts (omission errors) and responses to non-noughts or wrong-ear noughts (together constituting commission errors). Omission and commission errors were combined in a single expression (Index of errors $I_E$) derived from the formula (Pigache, 1976):

$$I_E = \frac{\text{Omission errors}}{\text{Total targets}} + \frac{2 \times \text{Commission errors}}{\text{Total non-targets}}$$

This score was also transformed logarithmically to expand the scale for parametric statistical analyses:

$$\log_{10} \left( \frac{I_E}{3 - I_E} \right)$$

in which $I_E$ results from adding the constant 1/2 (in order to avoid the impossible logarithm of zero) to both terms of the equation for $I_E$ (the effect of the transformations is shown graphically in Figure II.2). These procedures were applied to S1, F1, S2, and F2, with the resultant scores averaged to produce Mean $I_E$ ($M_{I_E}$) and Mean $I_E$ ($M_{I_E}$).

The error index combines omission and commission errors to produces scores relating to different performance strategies, as shown in Table II.1 (from: Pigache, 1976).

<table>
<thead>
<tr>
<th>Performance Strategy</th>
<th>Error Index ($I_E$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All targets correct (no errors committed)</td>
<td>0</td>
</tr>
<tr>
<td>50% targets correct (no errors committed)</td>
<td>0.5</td>
</tr>
<tr>
<td>All targets omitted (no errors committed)</td>
<td>1.0</td>
</tr>
<tr>
<td>Random throughout</td>
<td>1.5</td>
</tr>
<tr>
<td>All stimuli responded to</td>
<td>2.0</td>
</tr>
<tr>
<td>All stimuli except targets responded to</td>
<td>3.0</td>
</tr>
</tbody>
</table>

METHODS PARTICULAR TO INDIVIDUAL STUDIES

The methods described below are specific to Studies 1-4.

3.1 Study 1: Validation of the PAT

The methods below relate to results reported in Chapters IV, V, IX and X.
3.1 Subjects

Twenty male, chronic schizophrenic, patients participated in the study. A preliminary screen of patients in the long-stay wards of Friern Hospital identified 51 patients who were: (i) male; (ii) aged between 30 and 50 years; (iii) diagnosed as schizophrenic; (iv) ill for at least 2 years; (v) in good physical health; (vi) not given ECT or insulin therapy during the preceding 12 months; and (vii) who had prognoses suggesting that the current length of hospitalization would probably exceed the foreseen duration of the study (15-18 months). Twenty-nine of the 51 patients agreed to live in the Research Unit for a trial period. Nine returned to their original wards prior to the study. Of these patients one was reassessed as not schizophrenic, two were violent and disruptive, and six simply withheld their consent. Two of the patients (Nos. 2 and 8) were recruited later than the others.

3.1.2 Study Design

The study was a longitudinal comparison of CPZ and placebo conducted double-blind according to a cross-over design, and lasted 55 weeks (Figure II.3).
Patients were first matched as pairs and allocated to Group 1 or II. The match was based upon clinical status, IQ as tested by Raven's Progressive Matrices and the Mill Hill Vocabulary Test (Raven, 1958), and performance on the test battery used later to monitor change. They were then allocated to one of two initial groups (Groups 1 and 2) as 'matched' pairs. The list of matched-pairs was given to an independent pharmacist who 'blinded' the study by randomly allocating the members of each pair to different treatment groups: Groups I and II (the treatment code for each patient was sealed in an individual envelope in case of emergency). In this manner placebo was administered to each group over a period of 11 weeks (5 test-occasions) that was 'bracketed' by fortnights on 50% dose CPZ.

3.1.3 Medication

Special tablets of CPZ (100mg and 50mg) and placebo, all matching, were dispensed in fortnightly supplies for each patient. When patients consented to the study their medication was changed to CPZ tablets (as necessary). Two patients were treated with CPZ prior to the study and 18 were transferred from thioridazine, trifluoperazine, or fluphenazine decanoate to CPZ. A dose of CPZ equivalent to the prior neuroleptic dose was determined by the Unit's psychiatrists on the bases of the available literature and experience. For some patients the CPZ dose was further adjusted during the subsequent weeks. All patients were stabilized at their final dose.

![Figure II.3 Experimental design.](image-url)
level for at least two months before the experimental phase of the study. The final
dose for each patient is described as "100% dose CPZ". No other drugs were given
except for minor analgesics, antibiotics (as necessary) and an occasional extra dose of
100 mg CPZ (if essential, but not in the 24 h preceding a test-occasion). Extremely
high levels of compliance were achieved by the supervising nurses (further checked
by a tablet count at the end of each fortnight).

The study lasted 55 weeks. Patients of Group I continued to receive their
100% dose CPZ for the first 5 weeks of the study. The dose was then reduced to
50% for 2 weeks, followed by 0% (placebo) for 10 weeks, a reinstatement of 50%
dose CPZ for 2 weeks, and finally 100% dose CPZ for 36 weeks. Patients of Group
II continued on their 100% dose CPZ for the first 25 weeks, followed by 50% dose
CPZ for 2 weeks, placebo for 10 weeks, 50% dose CPZ for 2 weeks, and 100% dose
CPZ for the remaining 16 weeks of the study. The 50% dose CPZ was introduced to
minimise possible untoward effects of an abrupt change to placebo (c.f., Gardos and
Cole, 1978). Experimenters and psychiatrists knew when placebo would be substituted
for drug, but not for whom. The nurses' were 'blind' to both aspects and the patients
knew nothing about the placebo substitution.

3.1.4 Timing of Treatments and Test-occasions

The PAT was administered fortnightly (28 test-occasions) always one week
after each resupply of tablets (hence one week after any treatment change). In the
event of an apparatus breakdown tests were postponed by not more than one day.
Testing occurred in the morning at a fixed hour for each patient. Patients were
reminded to empty the bladder before the tests. All test-occasions began with the
PAT subtests given in constant order followed by a standard battery of other tests (not
reported here)^2.

3.1.5 Psychiatric Ratings

The methods described here refer to results reported in Chapters IV, V and X.
The same three psychiatrists (variously paired) rated throughout the study in relation
to each test-occasion (+ 1 day). The raters were prevented from referring to their
previous ratings. They rated in pairs according to the 16 item Brief Psychiatric Rating
Scale (BPRS) of Overall and Gorham (1962), and rated only the behaviour at the
interview. They discussed disparities between their ratings but finally rated

^2One of the behavioural tasks sought to measure incentive-motivation, since this was thought to be impaired in
schizophrenia (Rodnick and Garvey, 1957; Bullock, 1960). The results cannot be reported owing to technical difficulties. The
task is mentioned since it offered patients a cash reward, not exceeding £0.77 (enough at the time to buy a packet of cigarettes).
It was performed at the end of each test-occasion.
independently. The averaged item scores (each on a 0-6 scale) were analyzed according to the 5 factors in the ECDEU Manual (Guy, 1976), derived from a later 18 item BPRS (Overall, 1974). When applied to the earlier 16 item BPRS, the analyses of Factors II and IV lacked the future items 18 and 17, respectively (Table II.2). The factors were given equal weight by dividing each sum score by the number of constituent items. In addition, the factors were combined to produce 'Positive' (Factors III + IV + V) and 'Negative' (Factor II) symptom scores (Angrist, Rotroson and Gershon, 1980).

### TABLE II.2  BPRS Factors

<table>
<thead>
<tr>
<th>BPRS Factor</th>
<th>BPRS Item</th>
<th>BPRS Factor</th>
<th>BPRS Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor I</td>
<td>1. Somatic concern</td>
<td>12. Hallucinatory</td>
<td></td>
</tr>
<tr>
<td>(Anxiety-depression)</td>
<td>2. Anxiety</td>
<td>behaviour</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Guilt feelings</td>
<td>15. Unusual thought</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9. Depressed mood</td>
<td>content</td>
<td></td>
</tr>
<tr>
<td>NEGATIVE SYMPTOMS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor II</td>
<td>3. Emotional withdrawal</td>
<td>6. Tension</td>
<td></td>
</tr>
<tr>
<td>(Anergia)</td>
<td>(Activation)</td>
<td>7. Mannerisms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13. Motor retardation</td>
<td>17. Excitement*</td>
<td></td>
</tr>
<tr>
<td>18. Disorientation*</td>
<td>11. Suspiciousness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POSITIVE SYMPTOMS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Thought disturbance)</td>
<td>9. Grandiosity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Items missing from the BPRS version: Overall and Gorham (1962) as used in this study.

The psychiatrists also completed, jointly, a Global Rating of severity by marking a 100 mm analogue line labelled "As normal" to the left and "Totally psychotic" to the right, with the centre indicated. The score was the distance measured from the left. The scale was introduced late (on Week 13) when the need was recognized.

Neither the raters nor the researchers conducting the PAT knew of the others' results while the data were being collected.
3.1.6 Data Reduction and Statistical Methods

For Chapter IV

Plots for individual patients showed that, following CPZ reinstatement, the BPRS, Global Rating, and PAT variables would often recover slowly (up to 12 weeks for some patients). Hence, Group I patients had not fully recovered when Group II patients were transferred to placebo. The recovery of Group I was not complete until Group II reached its third placebo test-occasion. Thus, in order to use all possible data, while avoiding carry-over effects, data for the last three placebo occasions of each patient were averaged (i.e., Weeks 13, 15 and 17 for Group I; and Weeks 33, 35, and 37 for Group II). Similar averages were derived for the corresponding CPZ occasions (i.e., Weeks 13, 15 and 17 for Group II; and Weeks 33, 35 and 37 for Group I). Paired t-tests were used to compare the treatment effects, according to the two-period cross-over model described by Hills and Armitage (1979), which tests first for a treatment x period interaction and then, separately, for period and treatment effects. The same procedures were applied to 32 variables (reported here or in preparation). Spearman's rank correlation ($r_s$), Friedman's two-way analysis of variance by ranks, and the Mann-Whitney U-Test were also applied.

For Chapter V

The four PAT subtests were represented by $M_{L_e}$ (or $S_{1L_e}$ when $M_{L_e}$ lay close to its ceiling). Seven BPRS variables (Factors I to V, Positive Symptoms, and the Total BPRS: Table II.2) were reduced to four variables by disregarding Factors III to V (included in Positive Symptoms). The fifth variable was the Global Rating.

A further reduction of the five rated variables to one per patient was made post hoc by choosing the rating variable exhibiting the highest amplitude of fluctuations and the closest correspondence to the pattern of change shown by the PAT record.

3.1.7 Sustained Attention

The sustained attention results are presented in Chapter IX. The analysis of these data was performed according to the method of Study 4 (Section 3.4.4, below).

3.1.8 Response Latencies

The methods described here relate to results reported in Chapters IV and IX. Response latencies (RL) of correct responses (diotic targets only) were measured as a response variable and to verify that the latency criteria used to score errors (4.0 sec: slow subtests; and 1.5 sec: fast subtests) did not inflate the error scores with very late, but otherwise 'correct' responses, i.e. a possible confounding of errors with slow
responding. Accordingly, response latencies were measured using 'response windows' widened to 5 sec (S1) and 2 sec (F1) to admit possibly genuine responses with very long latencies. The latencies were measured from the onset of a metronome mark for 'nought' up to the onset of the response mark. Measurements were made for the diotic subtests only (the determination of very late 'correct' responses with the widened response windows became too ambiguous for the dichotic subtests). The latencies were transformed logarithmically for the statistical analyses to remove an observed significant correlation between the mean and variance.

3.2 Study 2: Neuroleptic Dose Escalation

The methods described here relate to results reported in Chapter VI.

3.2.1 Subjects

Ten of the twenty chronic schizophrenics recruited for Study 1 participated in this second study (i.e., Patients 1, 2, 3, 4, 7, 8, 10, 11, 14 and 18). The ten omitted patients comprised five who were discharged from hospital, two who were transferred at their request to other wards, Patient 15 who became depressed, and Patient 12 who had a long history of poor responses to neuroleptics. Two of the patients (Nos. 2 and 8) lagged behind the others because they were recruited late into Study 1.

3.2.2 Study Design

The test-occasions of Study 2 continued the fortnightly rhythm of Study 1 (always one week after each new supply of tablets). However, a short break (varying from 2 to 6 weeks) separated Study 1 from Study 2. During this period patients continued to receive their previous dose of CPZ ('100% dose CPZ'), given as unmarked tablets, but were not tested. Since there was no practice effect with the PAT (Chapter IV) the variable break was unlikely to produce differential effects.

The resumption of fortnightly testing initiated Study 2 which lasted 47 weeks. In this study CPZ was increased in dose, stepwise, from 100% to 200%, and then to 300% of the original dose (reaching 900 mg to 1800 mg per day). 'Blindness' to the study treatments was achieved by randomizing the durations of the run-in (100% dose CPZ) and terminal (300% dose CPZ) periods. The schedule produced consecutive observation periods, common to all patients, of 13 weeks on 100% dose CPZ, of 12 weeks on 200% dose CPZ, and of 21 weeks on 300% dose CPZ. There were too few patients to provide a parallel control group receiving 100% dose CPZ throughout.
3.2.3 Medication

Special tablets of CPZ (100 mg and 200 mg) and of placebo, all identical in appearance, were dispensed as fortnightly supplies for each patient. The 100% dose CPZ continued for the first 13 to 18 weeks, followed by 200% dose CPZ for 12 weeks, and finally 300% dose for 21 to 26 weeks. Orphenadrine was introduced during the 100% dose CPZ period of Study 2 and then maintained. It was not given 'blind'. Compliance was high and verified. No other drugs were given, except for minor analgesics and antibiotics (as necessary), and an occasional extra dose of 100 mg CPZ (if essential, but not in the 24 h before a test-occasion).

3.2.4 Procedures

The remaining procedures of Study 2 were the same as for Study 1 except that psychiatric ratings were not performed and PAT data only were scored.

3.2.5 Data Reduction and Statistical Methods

Descriptive data are presented for each individual. The statistical method comprised Wilcoxon's matched-pairs signed-ranks test.

3.3 Study 3: A Comparison of the PAT and CPT

The methods described here relate to results reported in Chapter VII.

3.3.1 Subjects

Eight of the ten chronic schizophrenic patients who participated in Study 2 (excluding two late patients who had not yet completed Study 2) agreed to being the subjects of Study 3 (i.e., Patients: 1, 3, 4, 7, 10, 11 and 18).

3.3.2 Medication

The medication of Study 2 was continued at the high (300%) doses of CPZ (900 mg to 1800 mg per day) which with orphenadrine (300 mg daily) had been stable for 23 weeks.

3.3.3 CPT Subtest

The four subtests of the standard PAT were augmented by the addition of two new subtests one of which represented the CPT. For these subtests the digits were read at the moderate (M) event rate of 1.0/sec (customary for the CPT) and were presented either diotically (M1: CPT) or dichotically (M2). The administration of one subtest per day also conformed to the standard CPT procedure. As previously, the 5
minute string of digits included 50 target 'noughts' spaced pseudorandomly. This resulted in an average relative target rate of 16.7%. Another digit always intervened between 'consecutive' noughts and a 2 sec window (from the onset of a metronome mark for 'nought') was allowed for 'correct' responses when scored by the PAT error index.

3.3.4 Timing of Test-occasions
Study 3 began one week after the eight participating patients had completed Study 2. Each patient performed all six subtests (administered one per day in a randomized order).

3.3.5 Data Analysis and Statistical Methods
In order to compare the randomized presentation order of S1, F1, S2 and F2 with the standard fixed sequence, the last test-occasion of Study 2 or its run-on provided the fixed sequence data for each patient.

The following statistical methods were used: Wilcoxon's matched-pairs signed-ranks test and Friedman's two-way analysis of variance by ranks.

3.4 Study 4: A Comparison of Schizophrenic and Healthy Subjects
The methods described here relate to the results reported in Chapter VIII.

3.4.1 Subjects
Study 4 compared the PAT performance of healthy subjects with that of chronic schizophrenics. Eleven healthy volunteers (nine male and two female aged 30 to 50 years) were recruited: five from the hospital nursing staff and six from members of the Neuropsychology Research Unit. The patients comprised the twenty chronic schizophrenics of Study 1.

3.4.2 Study Design
The patients underwent familiarization with the PAT procedures as described under General Procedures, above. The healthy subjects were tested once only on the full PAT. Their performance was compared to that of the schizophrenics as obtained on their first test-occasion.

3.4.3 Medication
None of the healthy subjects took any medication during the 24 h prior to the study. All the schizophrenics received CPZ as described for Study 1, above.
3.4.4 Sustained Attention

The methods described here relate to results reported in Chapter VIII and IX. In order to measure sustained attention the five-minute duration of each PAT subtest was divided into equal temporal thirds containing approximately equal numbers of targets. On all test-occasions the value of $I_E$ was calculated for each third of each subtest. The real $I_E$ value of each third was then replaced by its value as a percentage of all thirds summed. The percentage values were then analysed according to the algorithm of Chapter III in order to classify profiles of temporal $I_E$ change. Subjects with zero errors in all thirds could not be located in the algorithm and were logged separately.

3.4.5 Data Reduction and Statistical Methods

The four subtests of one test-occasion permitted a maximum of four observations per subject to lie within a relevant field, hence ordinal statistical methods were used to compare the groups (Mann-Whitney U-test). Wilcoxon's matched-pairs signed-ranks test was also applied.
CHAPTER III

An Algorithm to Classify Trends Relating to Sets of Three Observations

1 INTRODUCTION

A simple solution is offered, below, for the case of trends comprising three data points, when all subjects provide data at all three points and the values for each subject may be expressed as percentages of their sum. Examples include measurements of: performance during the three consecutive thirds of a task, to study patterns of vigilance change; performance during three related versions of a task, to identify sources of task difficulty; words correctly recalled from early, middle and late list thirds, to classify serial position effects; performance during low, medium and high levels of activation to determine peak arousal conditions; and of responses to three dose levels of a drug to identify a 'therapeutic window'.

All such percentage data lie within a three-dimensional space bounded by an irregular tetrahedron corresponding to one-half of a square pyramid sectioned vertically through a diagonal of its base (Figure III.1A). The coordinates of any point in this space are described by the three orthogonal axes X, Y and Z in Figure III.1B, where the origin of Z does not coincide with that of X and Y, but is inverted with respect to both and in effect bisects the X - Y projection line (hypoteneuse of triangle A + C). The triangles A, B and C of Figure III.1B are congruent with each other.

Each point in this space summarizes a unique set of relationships, depicted by three points and a connecting profile. The space contains all possible inflections between the profile segments. It is these profiles which must be reduced to a manageable number. This is achieved first by the simplification of reducing the three-dimensional space of Figure III.1 to two dimensions. The two-dimensional space comprises the triangles A and C with the common axis Z (Figure III.1B). Non-rectilinear grids are formed by orthogonal projections from the axes (Y and Z; X and Z) of these triangles. Viewed otherwise, the large triangle A + C is intersected by planes orthogonal to triangle B, with coordinates on the Z = 0-100% axis; hence all profiles within the three-dimensions of Figure III.1A are represented by points on the surface of triangle A + C. This representation exploits the fact that when the values of three quantities are expressed as percentages of their sum knowledge of any two percentages always implies the third.
An obvious way to reduce the number of profiles is to group them according to type. This step is often carried out subjectively and may be satisfactory when similarities and differences are strong, but is subject to bias in boundary cases. The better solution would be to apply a wholly objective algorithm as follows. The purpose of the algorithm is to classify all possible profiles as trends. It does not attempt to partition the variance specific to any particular set of data. The classification is achieved by dividing the surface of triangle $A + C$ into separate fields. Then all possible points (profiles) within each field are averaged to produce a representative trend (or pattern). Thus the data are replaced by the field trend and described by a field frequency.

A triangle may be divided into any number of fields, of any shape or size, according to arbitrary decisions. A more acceptable rule for the present algorithm is to divide the triangle into fields of equal area giving all possible profiles an equal chance of representation. The number of fields employed is a matter of personal choice depending upon the level of detail desired. The present 'seven-field algorithm partitioning a triangular surface' stipulates seven equal fields with one of them central.
(Constraint 1). There are several ways, however, to divide a triangle into seven equal fields as shown by Figure III.2. The fields of Figure III.2 were derived by trial and error together with the additional Constraint (2): that the fields should lie symmetrically about the axis projecting from the right angle to bisect the hypoteneuse (i.e., the $Z = 0$-100% axis). Subdivision as in Figure 2B was excluded by Constraint 3: that the field boundaries should intercept the sides of the triangle to divide them into thirds (explained later). The solution of Figure III.2C was excluded by two further constraints: that fields representing opposite patterns of error should not be contiguous with each other (Constraint 4); and that each peripheral field should possess a region transitional to the central field (Constraint 5). In the central field the average trend is an horizontal line connecting thirds of equal value.

![Diagram of three algorithms to subdivide a triangle into seven equal areas.](image)

**Figure III.2** Three algorithms to subdivide a triangle into seven equal areas. Triangles 2A, 2B and 2C represent different algorithms.

ALGORITHM

Coordinates for the field boundaries of Figure III.2A were derived using a triangle with 100 mm x 100 mm sides. Such a triangle has an area of 5000 mm$^2$ resulting in seven equal fields of 714.29 mm$^2$. The central field has sides with lengths of either 17.90 mm or 15.43 mm. The coordinates of Figure III.2A conform to the constraints listed earlier. Furthermore it was stipulated that the set of coordinates finally adopted should apply uniformly to all three axes X, Y and Z.

The 33.3% and 66.7% coordinates comply with Constraint 3 that each side of the triangle should be divided into thirds. Two thirds of each side contribute to angles of the triangle. Within each angle the trend is characterised by high values of one particular third (causing an inflection of the trend); the intermediate one-third of each side is a zone of transition between the angular patterns.
The problem was to determine the remaining coordinates and it was solved by trial and error. Initially, a mathematically neat solution was attempted. The field contours of Figure III.2A were derived by adding 50% and 25% coordinates to the axes, and the coordinates 16.7% and 8.3% (by using 2 and 4 as divisors of 33.3%). This did not yield fields of equal area. It proved necessary to adjust the four latter values to: 48.8%, 25.6%, 17.9% and 7.7% respectively. The resulting fields areas were estimated graphically and found to approximate the desired value of 714.29 mm², with an average 0.36% (± 0.87 mm²) error. The slightly inelegant coordinate values, above, result no doubt from demanding that the fields be of equal area, and from using the 'awkward' divisor 7 to partition the triangle.

The X and Y coordinates of the algorithm are shown in Figure III.3A, and the Z coordinates in Figure III.3B. Coordinates on the axis Z = 0-100% are not discrete points, but are stretched out along orthogonal projections to the X and Y axes; just as the coordinates of X and Y extend orthogonally from their axes as an imaginary grid. The points superimposed upon the projections of Figure III.3B coincide with those of Figure III.3A at all points where, in apparent open space, the field boundaries change direction. These points all lie on coordinates of the Z axis at selected intervals corresponding to those of X and Y; they indicate the influence of Z upon the fields' contours.

2.1 Example

An example will demonstrate how the algorithm functions. Suppose it is applied to a vigilance task with a possibility of errors in all temporal thirds. A graphical form of the algorithm may then be prepared as in Figure III.4, where (arbitrarily) the ordinate represents percent errors made in the last third (III) and the abscissa percent errors in the second third (II).³ Each point within the large triangle of Figure III.4 can accumulate the data of one or more individual subjects. At each point the data correspond to a unique profile of percent errors distributed over the sequential thirds of the vigilance task, as shown by the inset miniature graph (top right hand corner) of the figure. The average trend of each field is always the same as that depicted within the large triangle of Figure III.4. Accordingly, the data (or subjects) are classified by the field to which they relate. Subjects with zero values on all three axes X, Y and Z cannot be represented within the volume of Figure III.1A. They comprise an additional category and should be logged separately.

³Because the algorithm is symmetrical about the Z axis, with fields of equal area, it makes no difference to the relationships which coordinates are assigned to the three sets of data. However, the choice does affect the field identities and how their trends are interpreted. A sketch of the relevant relationships should be shown to clarify the situation.
Figure III.3 Coordinates of the seven-field algorithm. 3A. X and Y Axes. 3B. Z axis projected upon two dimensions. The closed circles are points of intersection with the X and Y projections of Figure 3A.

Usually, the fields would be labelled according to a meaning given by the experimental context. Within the inset triangle of Figure III.4 the fields were numbered from top to bottom and from right to left because the sequence of Fields
1 to 3 represents a progressively earlier onset of the vigilance decrement. In one study (submitted for publication) the data of schizophrenic subjects fell significantly more frequently within Fields 1 to 3, and less within Field 7, than those of healthy subjects; indicating that schizophrenics had greater difficulty with sustained attention.

In another study (manuscript in preparation using the same task and algorithm, the progressive occupation of Fields 1 to 3 by the data of schizophrenics correlated significantly with the patients’ state of clinical deterioration.

![Figure III.4](image)

**Figure III.4** Seven-field algorithm applied to subtest thirds. Temporal thirds of a vigilance task are represented by Roman numerals. The large triangle may be viewed as a graph plotting the scores of an error index ($I_E$) for the last (III) and second (II) thirds of the task, when expressed as percentages of ($I_E$) summed for all thirds (see miniature graph at the top right hand corner of the figure). The averaged trends of the seven fields are depicted. The field identity numbers are shown in the inset triangle.

### 2.2 Decision Matrix

A non-graphical expression of the algorithm may be obtained by first determining the slope and intercepts of each field demarcation line. A matrix of critical values may
ALGORITHM

then be created to determine the occupancy of a particular field. Thus the critical values of the Y axis applying to different ranges of the X axis was determined for the seven-field algorithm used in the foregoing example (Table III.1). Accordingly, in the table each range of X values is given a Roman numeral (matrix signature) and the critical values of Y applying to that range are presented. The occupancy of a particular field by any datum of the example is established as follows. The value (%) of the second (II) temporal third (X coordinate) is checked against all seven possible ranges of X values. It is matched with a range and thereby identified by a matrix number. The value (%) of the last (III) temporal third (Y coordinate) of the datum is then checked against all the critical values of Y listed under that matrix number. Whenever the value 'Y' of the datum exceeds a critical value of Y (as listed) it is given the score '1', and '0' when it does not. The combinations of '1' and '0' for the datum are then compared to the various combinations of the matrix (Table III.1) and the appropriate field is identified.

It should be noted that once the X value of a datum has been matched to a matrix number all other matrices are excluded and closed down (matrix numbers set to zero). Thereafter the Y value of a datum is compared within one matrix only. Also, when the location of an observed value ('X' or 'Y') coincides with a critical value, the matrix score (0/1) should be assigned at random and alternately, on the next occasion, when a value coincides with a field boundary. The matrices of Table III.1 provide the basis for a computer program.

3 DISCUSSION

This report began by depicting the tetrahedron occupied by triads of related data when expressed as percentages of their sum. It then derived an algorithm to describe and classify major composite trends within that space, and finally produced a decision matrix to define seven of them.

The algorithm is potentially useful whenever a treatment is applied at three different levels to the same individuals. Such data are not independent of each other, but it makes sense to explore their possible relationships and to give them meaning. The present algorithm should help in this task since it classifies all possible patterns of response.

Sometimes different patterns of response characterise different groups of subjects. A regression analysis might then show that the groups differ significantly. However a subsequent application of the seven-field algorithm would reveal the composition of trends contributing to the difference, which might prove more informative. Suppose instead that the group regressions did not differ significantly.
### TABLE III.1

Matrix signatures and critical values of the seven-field algorithm

<table>
<thead>
<tr>
<th>Matrix Nos. &amp; Critical Values&lt;sup&gt;2&lt;/sup&gt; of Y</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I) X &lt; 7.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Y &gt; 66.67</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2. Y &gt; 33.33 - X</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3. Y &lt; 33.33 - X</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>(II) X &gt; 7.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X &lt; 17.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Y &gt; 73.69 - X</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5. Y &gt; 25.61</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6. Y &lt; 25.61</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>(III) X &gt; 17.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>X &lt; 25.61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Y &gt; 73.39 - X</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>8. Y &gt; 48.76</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9. Y &gt; 48.76 - X</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10. Y &gt; 25.61</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11. Y &lt; 25.61</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>(IV) X &gt; 25.61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X &lt; 33.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>12. Y &gt; 66.67</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13. Y &gt; 48.76</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14. Y &gt; 33.33 - X</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15. Y &lt; 33.33 - X</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>16. Y &lt; 7.72 - X</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>(V) X &gt; 33.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X &lt; 48.76</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>17. Y &gt; 73.39 - X</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18. Y &gt; 17.90</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>19. Y &lt; 17.90</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(VI) X &gt; 48.76</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X &lt; 66.67</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Y &gt; 25.61</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>21. Y &gt; 73.39 - X</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>0</td>
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<tr>
<td>22. Y &lt; 73.39 - X</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(VII) X &gt; 66.67</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y &gt; 0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>1</sup> Numbered as in Figure III.4.

<sup>2</sup> Positive values only.
because of wide confidence intervals. The algorithm might nonetheless show a
difference when the comparison is restricted to the relevant field, or to a sector of
fields (as determined *a priori*). A different use would be to apply the algorithm
descriptively, to identify performance patterns *post hoc* but objectively in order to
generate hypotheses.

The algorithm yields nominal statistical data (counts per field) requiring non-
parametric analyses. It is recommended, however, that a scatter plot of the data is
inspected prior to any analysis in order to check the field distributions. A selection
of statistical tests is suggested, as follows. First, if prior meaning can be given to the
trends of one or several fields, it is legitimate to compare independent groups on the
frequency of profiles occurring for these fields. Suitable statistical tests would be the
Fisher exact probability test, or the $\chi^2$ tests for two and $k$ independent samples (e.g.,
Siegel, 1956). Second, when a *post hoc* question asks if subjects are distributed
differently between all seven fields, in order to generate hypotheses, the Cochran Q-
test may be applied (op. cit.); note that an eighth category may be necessary for this
test should numerous subjects with zero values at all measurement points be
encountered. Third, the distribution of subjects between several fields can be
correlated with an independent variable, such as severity of illness, using for example
the Contingency Coefficient (op. cit.). Lastly, the algorithm is not always limited to
nominal statistical methods. If the triad of observations is repeated for a fixed number
of trials, each subject may be represented by a field frequency score and ordinal
statistical tests become applicable. In addition, certain correlations may be suited to
the Spearman Rank Correlation Coefficient (op. cit.)

Limitations to the algorithm include the following. First, the algorithm
imposes cavalier decisions at field boundaries. This is inevitable when classificatory
methods are applied to a continuum. On the other hand, the present boundaries are
both objective and unbiased. Also, if sufficient observations occur within a field the
average trend becomes more probable, and boundary cases less equivocal. Second,
the algorithm eliminates all information concerning absolute performance levels.
However, once the classification has been made, it is possible to return to the original
data and to operate on the real values corresponding to the relevant field(s). Lastly,
a statistical analysis of field frequencies may be made invalid by a high proportion of
zero scores, because their exclusion would bias the sample.

The seven-field algorithm partitioning a triangular surface is a rigorous method
to categorise all sets of three percentage combinations. It may be adapted to
numerous classificatory purposes.
CHAPTER IV

Study 1: Clinical Relevance of the PAT

1 INTRODUCTION

This study was conducted to validate the PAT as a reliable and clinically relevant measure of schizophrenia, by demonstrating changes in both PAT performance and concomitant ratings when placebo was substituted for chlorpromazine (CPZ). The study was conducted between September 1971 and January 1973. Some of the results were presented as two preliminary communications (Pigache and Norris, 1973a; 1973b). This full report was published recently in a slightly shortened form (Pigache, 1993a). The methods are described in Chapter II (Sections 1, 2, and 3.1).

2 RESULTS

2.1 General

All patients were diagnosed as chronic schizophrenics. Their original diagnoses were: schizophrenic (4), acute schizophrenia (2), simple schizophrenia (6), paranoid schizophrenia (4), hebephrenic schizophrenia (3), and pathological personality (1). The study was conducted before the introduction of research diagnostic criteria. The demographic composition of the patient group is summarized in Table IV.1. Greater detail may be found in Appendix I. All patients were unmarried.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age at start of study</th>
<th>Chronicity since 1st diagnosis</th>
<th>Institutionalization (years)</th>
<th>Intelligence</th>
<th>ECT/Insulin1 treatments</th>
<th>Study CPZ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raven Mill Hill</td>
<td></td>
<td></td>
<td></td>
<td>ECT (n) Insulin (n)</td>
<td>Stablized Dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(months) (mg/day)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>39.0 (32-51) 16.5 (7-25)</td>
<td>8 (2-21)</td>
<td>&lt;85.0 (77-113)</td>
<td>8 6</td>
<td>7.0 (3-8)</td>
<td>500 (300-900)</td>
</tr>
<tr>
<td>II</td>
<td>42.5 (33-49) 16.0 (12-26)</td>
<td>14.5 (7-26)</td>
<td>&lt;85-122 (80-126)</td>
<td>8 6</td>
<td>8.0 (3-9)</td>
<td>500 (300-600)</td>
</tr>
<tr>
<td>I/II</td>
<td>40.5 (32-51) 16.5 (7-26)</td>
<td>11.5 (2-26)</td>
<td>&lt;85-122 (77-126)</td>
<td>16 12</td>
<td>8.0 (3-9)</td>
<td>500 (300-900)</td>
</tr>
</tbody>
</table>

1 Only one patient received neither treatment and the status of a second was uncertain. Values are medians (range)
The mean BPRS profile of the two groups at baseline (average of the first three test-occasions) closely resembled that of Overall and Rhoades (1982, Fig IV) for chronic schizophrenics on neuroleptics (Figure IV.1). A retrospective application of the DSM III criteria (American Psychiatric Association, 1980) would classify all the patients as "chronic schizophrenic: residual type (295.62).

Most patients received drugs other than CPZ prior to their stay in the Research Unit. The doses were converted to CPZ equivalents and readjusted as needed, before being stabilized. The final doses of CPZ were individualized and varied between 300 mg and 900 mg CPZ daily (grand mean 480 mg per day). The treatment details are shown in Table IV.1.

Few data were missing for any variable (< 1% of all test-occasions) except with the Global Rating Scale (see Methods). Three patients (Nos. 14, 15 and 17) were accelerated through the treatment schedule because of clinical deterioration (with the

**Figure IV.1** Profile of the BPRS item scores. Baseline scores (mean ± SEM) for the first three test-occasions when all 20 patients were stabilized on CPZ.
researchers kept 'blind') and missed one test-occasion each. Patients 14 and 17 missed their last two weeks of placebo, and Patient 15 the second period of 50% dose CPZ. Missing values were interpolated except when the next treatment differed from that of the missing value, in which case the prior value was extrapolated. No interaction or period effect approached statistical significance.

2.2 Clinical Ratings

2.2.1 Brief Psychiatric Rating Scale

Inter-rater reliabilities were tested twice: on the first ('early') and last ('late') test-occasions ('early' and 'late' in Table IV.2) when the patients received 100% dose CPZ (not necessarily test-occasions 1 and 28) and a pair of psychiatrists independently rated the patients. The correlations in Table IV.2 are based up (n < 20, because not all patients provided paired ratings on two well separated test-occasions. One rater "G" was present on 80% of all rating occasions and on all 62% of the occasions when two psychiatrists rated together. No rater was available on three of the 560 patient/occasions, and meaningful ratings could not be performed on five others, patient/occasions because of clinical deterioration. A high level of inter-rater reliability was maintained and all correlations were significant.

| TABLE IV.2 |
| Inter-rater reliability for total BPRS |
| Raters | No. Patients | Test-occasions |
|        |               | Early (t1) | Late (t2) |
| A & G  | 14            | 0.84***    | 0.97***    |
| F & G  | 12            | 0.96***    | 0.95***    |

*** p <.001.

Test-retest reliabilities (two consecutive occasions) were also estimated twice: on the first and last pairs of occasions when all patients were receiving CPZ (Table IV.3). Data on all three variables were available for all twenty patients. Global Ratings were not performed on test-occasions 2 and 3. All correlations were significant.

The effects of placebo substitution upon the BPRS are shown in Table IV.4. Four BPRS average scores were significantly greater under placebo than CPZ: the Total score, Positive Symptoms, Negative Symptoms, and Factor IV (Activation).
All subscores increased under placebo, but no increase amounted to one whole point of the 0-6 scales (no score became doubled).

The time-course of the BPRS Total Score responses, and the small effects (relative to the baseline) produced by the medication changes, are shown in Figure IV.2 (average of Groups I & II).

2.2.2 Global Rating Scale

Inter-rater reliability was not a factor with the Global Scale since the psychiatrists rated jointly. The test-retest reliability was estimated on 'late' occasions only, because the scale itself was introduced late. The correlation was significant (Table IV.3). The average Global score increased significantly, by 15.0% of the scale (a deterioration of 40.0%) under placebo, as compared to CPZ (Table IV.4). The time-course of the Global Scale responses, and the magnitude of effects (relative to the baseline, for Group II) produced by the medication changes, are shown in Figure IV.2.

2.3 The PAT

Test-retest correlations on both early and late test-occasions for Mean $I_{e}$ ($MI_{e}$) were significant (Table IV.3), indicating good reliability. There was no significant correlation between $MI_{e}$ and intelligence at baseline (mean of the first three test-occasions), as measured by either the Raven Progressive Matrices ($r_s$ -0.26) or the Mill Hill Vocabulary Test ($r_s$ 0.14). Trend analyses for practice (or boredom) effects over the first three test-occasions on 100% dose CPZ (Figure IV.3) showed no significant trend for any subtest or for $MI_{e}$ (Friedman two-way analysis of variance: n=20, df=2, $X^2_{12} < 1.3$).
The effects of substituting placebo for CPZ on the $M_{R}$ values of Groups I and II are depicted in Figure IV.4. The average $I_{R}$ values of all four subtests increased significantly under placebo. The greatest increases occurred with the more demanding subtests (S2, F1 and F2). Mean $I_{R}$ increased by 84.2% over the control CPZ value (Table IV.5). The increase of PAT errors was due to significantly more frequent omissions.

The contribution from commission errors was not significant. The increase of errors did not occur because the patients responded more slowly. On only three of the 504 test-occasions were response latencies longer than the 1.5 sec window allowed for a 'correct' response during F1 (and never more than that allowed for S1). Moreover, response latencies did not lengthen significantly when placebo replaced CPZ (Table IV.5). The time-course of $M_{R}$ responses and the magnitude of effects (c.f., the baseline) produced by the medication changes are shown in Figure IV.2 (average of Groups I & II).
**CLINICAL RELEVANCE OF THE PAT**

Figure IV.2 Comparison of time-course changes. Changes of $M_f$, the Global Rating score, and BPRS Total score, relative to the periods of CPZ and placebo treatments. The curves combine both halves of the cross-over study and all 20 patients. Note the scale expansions necessary to demonstrate the average effects with grouped data.
**Figure IV.3** PAT practice or boredom effects. Median scores of the first 3 test-occasions under 100% dose CPZ (n=20) for the four PAT subtests and the overall median.

**Figure IV.4** Values of $M_E$ with crossed-over treatments. Chronic schizophrenics of Group I (n=10) and Group II (n=10) were measured on fortnightly test-occasions for 55 weeks. Slow deterioration occurred when placebo was substituted for CPZ, and a similar slow recovery when CPZ was reinstated. Treatment changes were stabilized for one week before the PAT was administered on the next test-occasion.
CLINICAL RELEVANCE OF THE PAT

TABLE IV.5

PAT performance: effects of substituting placebo for chlorpromazine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range</th>
<th>Mean under CPZ</th>
<th>Difference placebo minus CPZ</th>
<th>% Change relative to CPZ value</th>
<th>p &lt; (df=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw Scores (means of all subtests)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omission errors</td>
<td>0-50</td>
<td>7.4</td>
<td>7.1</td>
<td>95.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Commission errors</td>
<td>0-325</td>
<td>3.0</td>
<td>2.3</td>
<td>76.7</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Index of Errors ($I_0^1$)</td>
<td>0-3</td>
<td>0.19</td>
<td>0.16</td>
<td>84.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean $I_e$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow diotic (S1)</td>
<td>0-3</td>
<td>0.14</td>
<td>0.04</td>
<td>26.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Fast diotic (F1)</td>
<td>0-3</td>
<td>0.16</td>
<td>0.16</td>
<td>100.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Slow dichotic (S2)</td>
<td>0-3</td>
<td>0.20</td>
<td>0.24</td>
<td>120.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Fast dichotic (F2)</td>
<td>0-3</td>
<td>0.26</td>
<td>0.19</td>
<td>73.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Response Latencies $^2$</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Slow diotic (S1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast diotic (F1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The difference scores were as described in the legend to Table IV.4.

$^1$ The $I_0$ transformations for logio were used in the analysis.
$^2$ Logio response latency was used in the analysis.

2.4 Correlations

2.4.1 Inter-subject Correlations

Each patient provided one test-occasion from which were taken all the variables cross-correlated in Table IV.6. The test-occasions were identified by using a table of random numbers, with resampling if any datum was missing (e.g., a Global Rating score). The analysis used Spearman's rank correlation method. Table IV.6 shows that $M_{I_e}$ values were significantly correlated with BPRS Negative Symptom scores. The scores of all three BPRS subscales were significantly correlated with the Global Rating scores.

2.4.2 Intra-subject Correlations

Only twelve of the 20 patients produced $M_{I_e}$ values in all three of the following ranges: 0 to 0.199, 0.2 to 0.399 and 0.4 to 0.599. In these cases, the Global Rating scores of those test-occasions that fell within the $M_{I_e}$ ranges, were averaged for each patient and range. The analysis used Friedman's two-way analysis of variance by ranks (n=12, df=2). The relationship shown in Figure IV.5 was significant.
TABLE IV.6
Cross-correlations between behavioural variables (r)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean $I_E$</th>
<th>Global Scale</th>
<th>BPRS Total</th>
<th>BPRS +</th>
<th>BPRS -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean $I_E$</td>
<td>0.30</td>
<td>0.17</td>
<td>0.23</td>
<td>0.50*</td>
<td></td>
</tr>
<tr>
<td>Global Scale</td>
<td>0.30</td>
<td>0.58*</td>
<td>0.54*</td>
<td>0.54*</td>
<td></td>
</tr>
<tr>
<td>BPRS Total</td>
<td>0.17</td>
<td>0.58*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS +</td>
<td>0.23</td>
<td>0.54*</td>
<td></td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>BPRS -</td>
<td>0.50*</td>
<td>0.54*</td>
<td></td>
<td>0.32</td>
<td></td>
</tr>
</tbody>
</table>

* p < .05 (two-tail)

FIGURE IV.5  Relationship between $M_E$ and Global Ratings. Ratings were always made on a day adjacent to the PAT administration. Twelve patients (Group I: Patients 3, 7, 9, 12, 17, 18, 19. Group II: Patients 2, 4, 14, 15, 16) yielded $M_E$ values in all three ranges of $M_E$ indicated along the abscissa. The histograms represent the mean ($ \pm $ SEM) of the Global Rating scores obtained for the same test-occasions.
The Global Rating scores increased at a lesser rate than did the increments of $M_E$ along the abscissa, especially at the highest $M_E$ interval. There were no significant correlations with the BPRS.

2.5 Hospital Discharge

Within six months of the study ending, four patients (Nos. 5, 9, 17 and 20) were returned to the community, and a fifth (Patient 13) with 25 years of schizophrenia (22 years as a hospital in-patient) was discharged to a supervised farm. The psychiatrists and social workers deciding on discharge knew nothing about the PAT results (these and the rating scale data were still in analysis).

Mean $I_E$, the BPRS Total, Positive Symptom and Negative Symptom scores, and the Global Rating scores, on the last three test-occasions were averaged for each patient. The values of each variable for the five patients discharged from hospital were compared with those for the fifteen patients retained, using the Mann-Whitney U-Test. Mean $I_E$ alone discriminated significantly between the two populations ($p < .05$). The average $M_E$ for the discharged patients was 0.03 (SD 0.016), whereas that for the patients kept in hospital was 0.39 (SD 0.370). The terminal $M_E$ and Global Rating values of all twenty patients are compared in Figure IV.6. The lower quartile cut-off score for $M_E$ was 0.06 and it separated patients fit for discharge from those who were not.

Three of the patients produced average $M_E$ values on the last three test-occasions greater than 0.06, but less than 0.10. Patient 16 ($M_E 0.095$) requested repatriation to British Guyana, and required a nurse to escort him there. Patient 15 ($M_E 0.088$) became severely depressed, and Patient 6 ($M_E 0.074$) was aggressively paranoid. Both were incapacitated by tardive dyskinesia. Neither was discharged from hospital.

3 DISCUSSION

Few would dispute that chlorpromazine is an effective drug in the treatment of schizophrenia. The present study demonstrated that, after substituting placebo for CPZ over a period of ten weeks, all four PAT subtest scores and $M_E$, the BPRS Positive, Negative, and Total Symptom scores and the Global Rating score, all deteriorated significantly. All the measures were reliable. The results therefore demonstrate that the PAT provided a valid and reliable measure of the severity of schizophrenic illness. This conclusion is supported by the correlations between $M_E$ and the rating scales. In addition $M_E$, alone, identified the patients who were later discharged from hospital. The BPRS was the least sensitive measure of change although it is used routinely in clinical trials of potential neuroleptics.
Before examining the results any further certain methodological aspects will be considered. First, slowness of response was not confounded with the observed increase of PAT errors. Second, there was no practice effect with the PAT during the first three test-occasions when such an effect would have been most evident. This
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agrees with results for the CPT (Latz and Kornetsky, 1965; Orzack et al., 1967; Benedict et al., 1994). Third, the test-retest reliability of the PAT was similar to reports for versions of the CPT (Rosvold et al., 1956; Landsell and Mirsky, 1964; Rutschmann et al., 1977). Fourth, $M_{I_{E}}$ did not correlate with the IQ measures. This agrees with findings for the CPT in centrencephalic epilepsy (Landsell and Mirsky, 1964) and chronic schizophrenia (Asarnow and MacCrimmon, 1978). It is also consistent with observations that IQ tests are insensitive to changes in the severity of schizophrenia (eg. Pearl, 1962; Depue et al., 1975; Martin et al., 1977; Aylward, Walker and Bettes, 1984). What the PAT appears to measure in schizophrenia will be the subject of a future report. Fifth, in placebo-controlled studies rater 'blindness' to drug treatments is always a question. In this study many patients deteriorated spontaneously several times (according to the ratings) hence any treatment guesses made by the raters were confused. Indeed, one might have wished for better results from the ratings had the 'blind' been broken by the effects of placebo!

The present result of increased PAT errors in schizophrenia following placebo substitution for neuroleptics appears to be the first of its kind. No similar observation are reported for the related CPT. However, omission errors on the CPT did decrease significantly when acutely ill schizophrenics were treated with carphenazine (Orzack et al., 1967) or CPZ (Spohn et al., 1977). No study has reported a significant change of commission errors in schizophrenia.

It important to note that the PAT, BPRS and Global Rating Scale all measured the same relapse of illness. The measures differed, however, in terms of their relative sensitivities to relapse. The BPRS Total score increased by 30.1%, the Global score by 40.0%, and $M_{I_{E}}$ by 84.2%, as compared to values under CPZ. The greater sensitivity of the PAT probably resides in the range of difficulty spanned by its four subtests. Thus one subtest is likely to lie at the upper limit of a patient's capacity and so will be sensitive to monitor change.

The increase of BPRS Negative Symptoms disagrees with claims that these symptoms are resistant to standard neuroleptics (Johnstone et al., 1978; Angrist et al., 1980). The correlation between these symptoms and $M_{I_{E}}$, however, was not fully representative of the data. Many examples could be given of Positive Symptoms clearly deteriorating in parallel to $M_{I_{E}}$ 'within' patients.

When the magnitude of deterioration is considered, the BPRS Total Score increased by 5.2% of its range and the Global score by 15.0%. The corresponding increase of $M_{I_{E}}$ is less easily stated. The theoretical upper limit of $I_{E} = 3$ was used conservatively in this study. However, this value applies only when all stimuli except targets are responded to. This perverse response to the instructions would require considerable skill by any subject. A more realistic upper limit (Pigache, 1976) may
be $I_g = 2$, achieved when all stimuli are responded to. This strategy was pursued for a time by Patient 8 during the slow subtests (he responded automatically), but he did not maintain it with the fast subtests. A more generally encountered upper limit is $I_g = 1$, which results from a total failure to respond (omission errors increased significantly). Thus, $M_{Ig}$ increased by 5.3%, 8.0%, and 16.0% of these ranges, respectively, when placebo replaced CPZ. More work is needed to establish the operational upper limit of $M_{Ig}$.

The Global Rating score was significantly correlated with the BPRS Total, Positive and Negative Symptom scores, and to $M_{Ig}$. However, the Global Rating Scale was barely sensitive to deterioration especially at high levels of $M_{Ig}$. When patients were severely disturbed, an increase in the severity of illness appeared to be more difficult to rate than a similar change at more moderate levels of illness. Somewhat better associations between the Global Rating score and $M_{Ig}$ could be seen in individual cases. Also, relationships between CPT errors and concomitant clinical ratings of schizophrenia were shown by Orzack et al. (1967) and Spohn et al. (1977).

The generally poor performance of the rating scales as measures of clinical change, and as scales to rank-order patients according to the severity of schizophrenia (as in the prediction of hospital discharge), was not due to the raters. The latter were teaching hospital psychiatrists whose ratings showed high levels of inter-rater and test-retest reliabilities. Often raters' standards may be comparable initially but drift apart with time, especially if the raters believe their accuracy is no longer checked (Romaczyk et al., 1973; Taplin and Reed, 1973). The early and late test-retest reliabilities indicated that this did not occur. It was also the raters who made the final discharge decisions. Criticism may be directed, instead, at the rating procedures. The raters may have been hampered by not seeing their previous rating scores. Also, the BPRS required that behaviour at the interview only should be rated, and was difficult to apply when patients were mute, withdrawn, or reluctant to describe symptoms (eg. hallucinations). The frequency of structured interviews taxed the raters' ingenuity to avoid repetition and might have trained the patients to return routine answers. Wistedt (1981) noted how "these patients are often difficult to rate with rating scales". The greater sensitivity of global scales (at the cost of specificity) is a common observation eg. Hollister and Kim (1982). However, the Global Rating score failed to predict hospital discharge reliably.

A more basic failing of the rating scales may reside at their lower poles where the concept of a 'normal' schizophrenic was scored as zero. This pole may not be well anchored. For example, Patient 10 (Figure IV.5) was mild mannered, well-dressed and withdrawn, and received a low Global score, yet he was amongst the most impaired on the PAT and was not discharged from hospital. The concept of 'normal'
might require a specific definition such as the ability to cope with normal everyday life, which in effect was embodied in the pragmatic discharge decision. Nonetheless, the ratings were sensitive to the treatment changes.

In contrast to the rating scales, the objective PAT variable: $M_{IE}$, correctly ordered the patients along a concrete dimension which measured more truly the severity of illness. In addition, the scores of eleven healthy subjects fell within the range of $M_{IE}$ 0 to 0.087 (Chapter VIII). This suggested that a cut-off score rounded to $M_{IE}$ 0.10 might indicate the upper limit of the normal range. The frequency of $M_{IE}$ values < 0.10, observed during test-occasions 1 to 25, was inversely correlated ($r$, 0.86, $p$<.001) to the magnitude of $M_{IE}$ averaged over test-occasions 26 to 28 (terminal $M_{IE}$ of Figure 3). Or, put another way, chronic and severe residual illness during the study (as measured by the frequency of $M_{IE}$ values > 0.10) 'predicted' that a patient would both remain in hospital and continue to produce high $M_{IE}$ values. Hence it was probably important that the $M_{IE}$ values used to 'predict' hospital discharge were averaged over three test-occasions (spanning four weeks). The ability to maintain a good performance would seem to be a factor that predicts a good outcome. A similar consistency was not observed in the rating scale data. These interesting results are no more than suggestive. They need to be confirmed by prospective studies.

In conclusion, the PAT has been validated as an objective measure of schizophrenic illness. It also provided the most sensitive measure of clinical relapse.
CHAPTER V

Study 1: Longitudinal Relationships Between Auditory Attention Task (PAT) Performance and Psychiatric Ratings

1 INTRODUCTION

It has just been shown that the PAT reliably monitored the effects of placebo substitution for chlorpromazine in schizophrenia, rank-ordered patients according to the severity of illness, 'predicted' hospital discharge, and correlated significantly with rating scales. The latter clinical relationship, however, was limited by the restriction that the data were taken from just one test-occasion sampled randomly per patient. Since the patients were evaluated fortnightly for more than one year much information was lost. Indeed, the quantity and detail of the available data probably exceed the provisions of any similar study. Thus the relationship of the PAT to clinical rating scales may be judged more critically by considering all test-occasions.

Unfortunately, the quantity of data collected creates a problem of analysis. The Author is unaware of any statistical method correlating two time-series each comprising auto-correlated data. Accordingly the results of Study 1 will be presented individually for each patient. The reader is invited to compare the PAT with the rating scales visually. This mode of analysis conforms to time-honoured clinical practice. Three validation criteria apply to the PAT: an increase of errors following placebo substitution for chlorpromazine; a relationship to the rating scales; and the 'prediction' of hospital discharge. The relevant methods are described in Chapter II (Sections 1, 2, and 3.1).

2 RESULTS

There was little redundancy when determining the rating variable to select per patient. Nine patients yielded one option each, another nine offered two each, and two patients provided four variables each. The profiles of all remaining ratings were generally of low amplitude and saw-toothed in appearance. Accordingly, each patient will be considered in relation to the rating variable most closely matching the PAT data. In Figures V.1 to V.7 the correspondence of profiles is more meaningful than the 'absolute' values of the scores.4

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4 In Chapter IV it was shown that the rated severity might not be a reliable measure since it did not 'predict' hospital discharge during the subsequent six month; whereas the MIx values did so with complete accuracy.
2.1 BPRS Factor I

Three patients (Nos. 4, 6 & 17) showed increases of 'anxiety-depression' which related to PAT scores (one case is shown). The increase of this factor for Patient 17, after placebo substitution for CPZ, closely matched his $M_E$ values (Figure V.1). Note the greater baseline stability of $M_E$. The Global Rating (not shown) lacked too many data early in the study for a full match. The discharge of this patient from hospital, soon after the study, was predictable from his low $M_E$ values on the last three test-occasions.

![Graph showing Chlorpromazine % and BPRS variables over weeks]

**Figure V.1** Relationship between $M_E$ and BPRS variables. Patients 15 and 17: $M_E$ (solid circles). Patient 17: BPRS Factor I (open circles). Patient 15: BPRS Positive Symptoms (open circles). The missing observations for the last placebo occasion of Patient 17, likewise the second 50% dose CPZ occasion of Patient 15, resulted from the patients' deterioration. Consequently a psychiatrist broke the code then brought forward the next scheduled treatment.
2.2 BPRS Positive Symptoms

Seven patients (Nos. 5, 8, 9, 12, & 14-16) produced increases of Positive Symptoms corresponding to $M_E$ (four cases are shown). The increase of these symptoms for Patient 15 at the end of the placebo period provided a very good match with his $M_E$ values (Figure V.1). Note the greater baseline stability of $M_E$. The Positive Symptoms changed more than the Total BPRS score (not shown). It is interesting that the $M_E$ peak at Week 51 resulted after the patient had been transferred to a locked ward, where his medication was suspended for one week without authorization!

Patient 8 deteriorated after one week of treatment with 50% dose CPZ (Figure V.2). He relapsed further under placebo, but began to improve by Week 25 after 100% dose CPZ had been reinstated. He then oscillated considerably for 22 weeks, with his lowest $M_E$ values scarcely better than his deterioration at week 7 (under 50% dose CPZ). At Week 51 his $M_E$ values began to increase dramatically as he attempted a strategy of responding automatically to every digit (slow subtests: the strategy was not sustainable with the fast subtests). This relapse on 100% dose CPZ continued for 12 weeks then recovered spontaneously (Chapter VI). Little of this behavioural flux was reflected in his ratings. His Positive Symptoms are shown simply because they varied the most.

A rather paradoxical record is that of Patient 12 (Figure V.2). He was reputed to be resistant to neuroleptics. His $M_E$ values appeared to improve as a function of time, from his first high peak (50% dose CPZ), but the trend was labile. Curiously, the peaks and troughs in the Positive Symptom profile coincided with opposite patterns in the Negative Symptoms. The Global Rating (not shown) also improved with time, but lacked too many early data for a full match.

Patient 13 remained fairly stable in terms of $M_E$ (Figure V.2). His Positive Symptoms are shown because they varied the most. His condition possibly improved during the second half of the study. The PAT, BPRS and Global Rating variables also indicated that the patient fluctuated little. Despite an average rated global severity of about 40% this patient was discharged from hospital, in keeping with his low $M_E$ values (c.f., Patient 17).

2.3 BPRS Negative Symptoms

Six patients (Nos. 5, 7, 9, 11, 19 & 20) deteriorated 'significantly' in terms of Negative Symptoms (three are shown). For Patient 9 these symptoms (Figure V.3) changed more markedly than his Positive Symptom, Total BPRS, or Global Rating
Relationship between $M_{\text{fg}}$ and BPRS Positive Symptoms. Patients 8, 12 and 13: $M_{\text{fg}}$ (solid circles) and BPRS Positive Symptoms (open circles). Patient 8 was not rated on his penultimate test-occasion.
Figure V.3 Relationship between $M_{Ig}$ and BPRS Negative Symptoms. Patients 9, 11 and 19: $M_{Ig}$ (solid circles) and BPRS Negative Symptoms (open circles). Patient 19 was not rated on his first test-occasion.
scores. Later this patient was discharged from hospital, in keeping with his low $M_{T_e}$ values (c.f., Patient 17). Only the Negative Symptoms changed significantly for Patients 11 and 19 (Figure V.3). The figure shows a very good correspondence between the PAT and BPRS measures during both the placebo phase and the reintroduction of CPZ. Note the stability of the $M_{T_e}$ baseline. The ratings of Patients 9 and 11 were rather high at the outset of the study and then declined.

2.4 Global Rating Scale and Total BPRS

Fifteen patients (i.e., all except Nos. 2, 8, 11, 13 & 19) registered changes in terms of Global Ratings or Total BPRS scores which were related to PAT variables (twelve are shown).

The patients (Nos. 7, 14 & 16) of Figure V.4 show very good relationships between $M_{T_e}$ values and Global Ratings when placebo was substituted for CPZ and after the drug was reinstated. Patient 7 deteriorated sharply from a low and steady baseline in terms of BPRS Negative Symptoms. However, he became mute and unrateable in the period just after placebo, hence only his Global Ratings are depicted in Figure V.4.

Patients 14 and 16 also showed changes of BPRS Positive Symptoms, nearly as dramatic as their Global Rating curves in Figure V.4. It is interesting that Patient 14 produced an $M_{T_e}$ peak on Week 27 (50% dose CPZ) the day after hearing of his father’s death. The ratings did not reflect this.

The patients (Nos. 1, 6 & 10) of Figure V.5 indicate somewhat different associations between the PAT and Global Rating or Total BPRS scores. With Patient 6 just before and during placebo the $M_{T_e}$ profile was generally similar to that of the Total BPRS, but deterioration with placebo was evident only for the PAT. The amplitude of change was quite small in each case. The BPRS Factor I received its highest rating for this patient on the last placebo occasion, but the whole record fluctuated considerably. This patient was discharged from hospital (c.f., Patient 17).

The associations, above, for Patients 1 and 10 are less evident with respect to $M_{T_e}$ (profiles: Figure VI.3) because their values lay close to $M_{T_e}$ 1.0 (no responses). Accordingly, the Global ratings for these patients in Figure V.5 are related to the easiest subtest (S1$e$). The figure shows that Patient 1 deteriorated markedly under placebo with respect to both $M_{T_e}$ and the Global Rating. The relationship was similar for Patient 10 but of lesser amplitude.
Figure V.4 Relationship between $M_{fg}$ and Global Rating scores. Patients 7, 14 and 16: $M_{fg}$ (solid circles) and Global Rating scores (open circles). The Global Rating Scale was introduced late on Week 13. The missing observations for the last placebo occasion of Patient 14 resulted because of the patient’s deterioration. A psychiatrist broke the code then brought forward the next treatment.
Figure V.5  Relationship between $M_{1g}$ or $S_{1g}$ and rating scores. Patients 1 and 10: relationships between $S_{1g}$ (solid circles) and Global Rating scores (open circles). Patient 6: relationship between $M_{1g}$ (solid circles) and Total BPRS scores (open circles). The Global Rating Scale was introduced late on Week 13.
2.5 Unassociated Ratings

The patients (Nos. 2, 4 & 18) of Figure V.6 again show very clear deteriorations of $MI_E$ following placebo, but this time without associated rating changes. The Global Rating of Patient 18 is shown because a peak (Figure V.6) coincides with the last placebo occasion and the subsequent trend indicates improvement. The BPRS ratings were saw-toothed with no trend. Patient 2 became mute and unratable when $MI_E$ peaked on the last placebo occasion, possibly manifesting clinical deterioration. Otherwise his ratings were as flat as in Figure V.6. Patient 4 was unusual because the raters detected no change resulting from placebo. Later they did observe a deterioration (equally present with the BPRS Factor I) which overlapped the $MI_E$ peak on Week 51 (Figure V.6). Note the baseline stability of both variables.

2.6 Anomalous Ratings

Figure V.7 depicts patients (Nos. 3, 5 & 20) who were variously anomalous. Thus Patient 3 deteriorated late (Week 25) and dramatically, according to both $MI_E$ and the Global Rating Scale, and well after 100% dose CPZ was restored. His $MI_E$ baseline had been remarkably stable for at least five months. His relapse continued for a total of 100 weeks then spontaneously recovered (Chapter VI). Patient 5 also deteriorated late according to $MI_E$ when 50% dose CPZ was reintroduced, and two weeks later according to the rating scales. Figure V.7 shows that both $MI_E$ and the Total BPRS remained stable for at least 39 weeks before increasing together and subsiding likewise. Similar patterns were obtained for this patient with ratings of BPRS Positive and Negative Symptoms and the Global Scale. This patient was later discharged from hospital, as was consistent with his $MI_E$ values (c.f., Patient 17). Patient 20 was the only case to show a rated deterioration during the placebo period without any concomitant change of a PAT variable. The Global Rating score increased (Figure V.7) and to a lesser extent so did the BPRS Negative Symptom score (not shown). During this period he decided to marry a patient 20 years his senior and on his own initiative took the necessary steps at the registrar's office. His discharge from hospital (c.f., Patient 17) was 'predicted' by his terminal $MI_E$ performance, but not by the rating scores which did not recover.
Figure V.6 Relationship Between $M_{Li}$ and Global Rating scores. Patients 2, 4 and 18: $M_{Li}$ (solid circles) and Global Rating scores (open circles). The Global Rating Scale was introduced late on Week 13. One rating late in the series was missing for Patient 2 and "U" indicates unratable.
Figure V.7 Relationship between $M_L$ and Global Rating or Total BPRS scores. Patients 3 and 20: relationships between $M_L$ (solid circles) and Global Rating scores (open circles). The Global Rating Scale was introduced late on Week 13. Patient 5: relationship between $M_L$ (solid circles) and the Total BPRS score (open circles).
3 DISCUSSION

It really does seem remarkable that performance errors on a test of auditory sustained attention should show any relationship at all to schizophrenic symptoms evaluated by independent psychiatrists under double-blind conditions. Yet a very good correspondence was evident in the data. The graphical presentation of longitudinal data from each case supplements the statistically significant correlations reported in Chapter IV and is far more telling.

It should not be concluded, however, that PAT data are made redundant by the observed relationship to rating scale findings. Two reasons alone justify giving more weight to the PAT findings. First, the PAT was more sensitive to deterioration than the rating scales when the dose of CPZ was reduced, or replaced by placebo (Chapter IV). Second, when patients became mute and unrateable an exacerbation of the illness could only be inferred from the unobtainable ratings; whereas the PAT provided continuous measurements.

From a research point of view unrateability comprises a loss of data. With the PAT the baseline observations established that the patient was cooperative. Thus subsequent omission errors were interpreted as clinical deterioration, given continued cooperation (indicated by postural readiness, sporadic responses, etc.). Accordingly, omission errors were less ambiguous than unrateable behaviour.

The sensitivity of the PAT to clinical deterioration can be increased by considering solely subtest(s) lying at the limits of a patient's ability. Thus for Patients 1 and 10 who were severely ill the only subtest manageable was the easiest (S1); the other subtests lay at the ceiling of performance. For other patients (notably Nos. 4, 5, 6, 9 & 13) only the dichotic subtests taxed their capability, whereas the remaining subtests (not shown) lay at the floor of performance.

The rating scales were less sensitive than the PAT. Global Rating Scale was clearly the scale most closely related to the PAT (13/20 patients showed change) despite the absence of a statistically significant correlation (Chapter IV). Global rating scales are commonly more sensitive than specific symptom scales (Hollister and Kim, 1982), but also less specific. Nonetheless, the Global Rating score failed to predict hospital discharge reliably (Chapter IV). The BPRS was even less sensitive to changes in the severity of illness, although it is used routinely for clinical trials of neuroleptic drugs.

Another difficulty with rating scales occurs when different scales or factors do not fully agree with each other as was observed here. Which result should one accept? The choice could be biased. Such a problem does not arise with the PAT since $M_{Le}$ is the primary measure.
The disparities noted between the rating scales and the PAT raise important questions of validity. The rating disparities were not entirely due to rater error or to the rating methodology, as discussed in Chapter IV. So why did the patients differ as to which rating scale factor(s) most closely related to PAT performance? With schizophrenics the PAT primarily measures sustained attention (Chapters VIII & IX). When performance is impaired attention is diverted from the task and sustained attention appears to be deficient. Thus one possibility is that almost any symptom of schizophrenia might distract attention. Perhaps it is only symptoms above a certain threshold of severity (inaccurately estimated by rating methods) which cause PAT performance to deteriorate appreciably. However, a simple assumption that rateable schizophrenic symptoms are necessary to cause impaired sustained attention is difficult to reconcile with the present findings. Many peaks of PAT impairment (e.g., for Patients 4 & 8) were not represented by concomitantly high ratings. Perhaps certain symptoms were less rateable than others, or they were difficult to elicit during a formal interview. As noted, some patients were at times unrateable.

Alternatively, a more fundamental process may be involved. The worsening of this underlying defect would both impair sustained attention and produce the symptoms of schizophrenia. Independently, the symptoms themselves might also divert attention further and thereby exacerbate the performance deficit.

With respect to the severity of illness, the PAT (with its high test-retest reliability) would seem to be the more valid of the methods, since it mapped the effects of treatment changes more closely than any rating scale. Moreover, the example of Patient 20 indicates that when schizophrenic symptoms deteriorate, without causing PAT errors to increase, a patient may still be able to behave coherently and leave hospital. Perhaps a continuing ability to focus attention voluntarily, and to hold the focus, is a prerequisite for coping with everyday life.

With respect to diagnostic specificity, however, the profile of symptoms would constitute the relevant parameter, since conditions other than schizophrenia can impair PAT performance. By this evaluation Patient 20 remained schizophrenic even though discharged from hospital.

It is concluded therefore that the PAT provides a valid and reliable measure of the severity of schizophrenia.
CHAPTER VI

Study 2: Effects of Placebo, Orphenadrine, and Rising Doses of Chlorpromazine on PAT Performance in Chronic Schizophrenia. A Two Year Longitudinal Study

1 INTRODUCTION

Previously, twenty chronic schizophrenic patients consented to participate in Study 1, which would determine how much CPZ they needed, or if they needed the drug at all. All required CPZ, but the question was incompletely answered for fifteen patients who remained in hospital. Was their inadequate therapeutic response the best they could achieve (Ayd, 1975), or were their dosages too low? These patients were invited to spend a second year in the Research Unit during which time the dose of CPZ would be increased (Study 2). Ten patients agreed to do so. The second drug (orphenadrine) was added as a prophylactic against the extra-pyramidal effects of CPZ. Orphenadrine like CPZ (Snyder, Greenberg and Yamamura, 1974) has anticholinergic and antihistaminic properties. It was impossible to persuade the psychiatrists to rate fortnightly for a second year. Data will be presented for each individual patient and span the two years of both studies. The results reported here were published recently (Pigache, 1993b). The methods are described in Chapter II (Sections 1, 2, and 3.2).

2 RESULTS

2.1 Effects of increasing the dose of chlorpromazine

The $M_{f}$ values of Patients 1, 2, 3, 8, 10, and possibly of Patient 14, improved during Study 2 (Figures VI.1 to VI.4). This improvement began during the initial period of continued 100% dose CPZ and appears unrelated to the subsequent dose increments. However, the average $M_{f}$ value of the first three test-occasions of Study 2 under 100% dose CPZ did not differ significantly from that of the last three test-occasions under either 200% dose CPZ or 300% dose CPZ, when all patients were considered (Wilcoxon's matched-pairs signed-ranks test). Note that the increases of CPZ dose did not impair the performance of any patient.

2.2 Effects of orphenadrine

The average $M_{f}$ value of the three test-occasions preceding orphenadrine 300 mg per day (Figure VI.5) did not differ significantly from that of the three that followed (Wilcoxon's matched-pairs signed-ranks test). Nor did orphenadrine account for the improvement of individual patients.
Figures VI.1 Longitudinal values of $M_L$ for Patients 3 & 8. Observations over 26 months corresponding to four weeks observation each. Studies 1 and 2 were separated by a break from testing (as indicated). The substitution of placebo for 100% dose CPZ, and the dose increases of CPZ, are depicted along the top of each figure. The arrows indicate the start of orphenadrine 300 mg per day, which continued for the rest of Study 2.

Figure VI.2 Longitudinal values of $M_L$ for Patients 7, 11 & 18. See legend to Figure VI.1.
Figure VI.3  Longitudinal values of $M_d$ for Patients 1, 2, 4 & 10. See legend to Figure VI.1.

Figure VI.4  Longitudinal values of $M_d$ for Patient 14. See legend to Figure VI.1.
Mean IE

Patient number

-5 -3 -1 +1 +3 +5

Weeks

Figure VI.5 Effects of orphenadrine. Comparison of the $M_{E}$ values of the 3 test-occasions preceding the introduction (arrow) of orphenadrine 300 mg per day (as a supplement to 100% dose CPZ) with the 3 test-occasions after, for the nine available patients. There was no significant effect upon performance.

2.3 Patterns of relapse

The results shown in Figures VI.1 to VI.4 show the PAT performances ($M_{E}$) of all ten schizophrenics over more than two years (Studies 1 and 2). Four types of relapse with different time-courses (some recovering) can be discerned in the data. These are described next.

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5 Patients 2 and 8 lagged behind the others in terms of the treatment schedules. This departure from the study routine resulted in two errors. Patient 2 began orphenadrine too early (with no pre-drug observations). Also, a box with polygraph recordings of these two patients disappeared during a laboratory reorganization.
2.3.1 Placebo-induced relapse

Four patients (Nos. 7, 8, 11, and 18) of five with a baseline of 3 observations during 100% dose CPZ (Figures VI.1 and VI.2) relapsed when placebo was substituted for CPZ. Patient 8 had already deteriorated after one week of treatment with 50% dose CPZ. Patient 3 deteriorated 7 weeks after the placebo period, during 100% dose CPZ. All five patients, with a baseline of 13 observations during 100% dose CPZ, relapsed after placebo substitution or when 50% dose CPZ was given for the second time. Patient 14 (Figure VI.4) deteriorated following one week of 50% dose CPZ after hearing of his father's death the day before testing. The deteriorating $M_{IG}$ values of Patients 1 and 10 during placebo in Figure VI.3 appear to continue earlier trends, but they mask clear relapses of $SI_{EG}$ induced by placebo (Figure V.5). Subtest S1 lay just within the patients' capacity and, by the time that placebo was introduced, they seldom responded to the other subtests (c.f., $M_{IG}$ values of approximately 0.75 just prior to placebo in Figure VI.3). The average $M_{IG}$ value (0.26) of the last three test-occasions under 100% dose CPZ differed significantly from that under placebo (0.56) for these ten patients ($p < .01; T=1$, Wilcoxon's matched-pairs signed-ranks test, two-tail). The time-course of relapse was either gradual or followed a long latency.

All nine patients, whose performance ($M_{IG}$ or $SI_{IG}$) deteriorated during placebo, improved when 100% dose CPZ was reinstated (Patient 8 did so only transiently, Figure VI.1). The improvement was gradual except for two cases of late relapse (Patients 2 and 4) who improved rapidly.

2.3.2 Long-period relapse

The pattern considered here is one of relapse and partial recovery spanning about one year that was shown by five patients. Patient 3 (Figure VI.1) relapsed on Month 6 of Study 1, deteriorated further over 18 weeks, and reached an asymptote that continued for 26 weeks. His subsequent improvement reached its nadir of errors 26 weeks later, but was unstable. Both the deterioration and the onset of improvement took place during 100% dose CPZ. This patient's deterioration was unexplained (spontaneous).

Patient 8 relapsed under placebo, improved on 100% dose CPZ at Month 7 (Study 1) then oscillated considerably for 22 weeks, with his best $M_{IG}$ values scarcely improving upon the deterioration at Month 2 (under 50% dose CPZ). On Month 13, $M_{IG}$ increased dramatically when the patient attempted a strategy of responding automatically to every digit. This was not sustainable with the fast subtests. Improvement progressed over the subsequent period of 26 weeks, largely due to his abandoning the metronomic strategy at Month 1 (Study 2) with a drastic decrease of
commission errors. This entire phase of relapse and the start of recovery occurred during 100% dose CPZ and was not explained (spontaneous). Improvement continued under higher doses of CPZ and finally oscillated between $M_E$ values similar to the first two months of Study 1 (including 50% dose CPZ).

Patients 1 and 10 (Figure VI.3) showed a pattern of long-period relapse and partial recovery under 100% dose CPZ: from Month 4.5 of Study 1 to Month 3 of Study 2 (continuing for Patient 10), but this included the placebo period. Patient 2 (Figure VI.3) showed a similar pattern: from Month 3 of Study 1 to the end of Study 2, but his data are incomplete.

2.3.3 Enduring relapse

A pattern of gradual deterioration over the two years is as an underlying trend for all patients (Figures VI.1 to VI.4), with the possible exceptions of Patients 2 and 14 (Figures VI.3 and VI.4) whose trends are slight. The average $M_E$ value (0.18) of the first three test-occasions of Study 1 differed significantly from the value ($M_E$ 0.32) of the last three test-occasions of Study 2 ($p < .01$: $T=0$, Wilcoxon's matched-pairs signed-ranks test, two-tail)

2.3.4 Short-period relapse (lability)

All ten patients showed a pattern of labile, short relapses (with recovery), over the two years. This was less marked for Patients 4 and 11 (Figures VI.2 and VI.3). Such an oscillating pattern may be expected with repeated measurements, due to subject variation (e.g., fatigue and life-events) and to error of measurement. However, the latter error was probably low, since Patients 3, 4, and 11, and many others (unpublished data) showed long stretches of stability across test-occasions.

3 DISCUSSION

The ten schizophrenics studied were quite representative of chronic, refractory patients needing long-term institutional care, who respond insufficiently to standard doses of neuroleptics. Such patients are often switched to higher doses or to more potent drugs (Collins, Hogan and Awad, 1992). Despite their poor responses to chlorpromazine they did appear to benefit from the drug (300 mg to 600 mg per day) i.e., all relapsed under placebo (with the exception of Patient 3). However, their PAT performance was always deficient. At the end of Study 2 none attained the cut-off score of $M_E$ 0.10, which indicated a potential for hospital discharge (Chapter IV).

Increases of CPZ dose, beyond the original 100% dose CPZ level (established clinically), did not improved PAT performance. Those patients who later improved
began to do so before the dose was increased. The conclusion agrees with that of Baldessarini, Cohen and Teicher (1988). It cannot be argued that the final doses (CPZ 900 mg to 1800 mg per day) were not high. They were somewhat higher than suggested by Baldessarini and Davis (1980) and virtually the same as proposed by Pi and Simpson (1981): "if the choice of drug is chlorpromazine, we would recommend a maximum upper limit of 1600 mg/day. Such an amount is required on rare occasions, and indeed most cases respond to 400-700 mg/day". The last recommendation was supported by the present results. Baldessarini and Davis (1980) cited two "rare" clinical trials (Prien, Cole and Belkin, 1969; Prien, Levine and Cole, 1969) which compared moderate and high doses of phenothiazines, equivalent to 300 mg and 1500 mg CPZ per day, in the same populations. They concluded from these that "clinical advantages may not be found regularly at doses above the equivalent of 300 mg CPZ a day". This is consistent with the present results.

It is remarkable, however, that very high doses of CPZ did not impair PAT performance. This does not support a hypothesis of Baldessarini et al. (1988) which predicts a biphasic response to neuroleptics as the dose is increased. Since $M_i$ values were correlated with ratings of behaviour (Chapters IV & V) the present results also contradict the conclusion of Dahl (1986) that high plasma concentrations of CPZ, or haloperidol, may cause behavioural deterioration. Thus nothing was either gained or lost, behaviourally, from the very high doses of CPZ. Such treatment, however, does expose patients to the risk of serious somatic side-effects. This argues against policies advocating high dose neuroleptic treatment (McCreadie and MacDonald, 1977; Brotman and McCormick, 1990).

Orphenadrine did not alter PAT performance when added to 100% dose CPZ. Reports by Tune et al. (1982) and Perlick et al. (1986), that anticholinergic drugs impaired recall by schizophrenics, relied upon correlations between memory performance and serum drug concentrations (significant but low). The results were consistent with the known effects of anticholinergic drugs in healthy and schizophrenic subjects (review: Spohn and Strauss, 1989). PAT performance does not depend upon memory. It did correlate, however, with the rated severity of schizophrenia and it 'predicted' hospital discharge (Chapter IV). Clinical ratings of schizophrenia were unaffected by anticholinergic drugs in studies reviewed by McEvoy (1983), which is consistent with the PAT result. One study (Johnstone et al., 1983) claimed that procyclidine added to flupenthixol treatment retarded the improvement of positive symptoms in acutely ill schizophrenics. This was observed between weeks 4-6 after procyclidine treatment, but not between weeks 7-9. The statistical analysis made 72 comparisons and yielded ten one-tail significances. It is difficult to judge these effects
since the number of patients varied between symptom clusters. However, if the adverse effects of procyclidine were real they were also transient.

Four types of relapse were observed. The first was an acute schizophrenic episode induced by substituting placebo for CPZ. This is a robust effect and was exploited to validate the PAT (Chapter IV). Placebo appeared not harm PAT performance permanently. However, recovery took months in many cases to approach the pre-placebo level, after 100% dose CPZ was resumed. Such slow recovery might underlie reports that some schizophrenics fail to recover their former psychiatric status when drug is reinstated after neuroleptic withdrawal (Carpenter, Rey and Stevens, 1980; Branchey et al., 1981; Pyke and Seeman, 1981; Johnson, 1990, review). Perhaps the observations did not continue long enough. The sometimes long duration of relapse after drug withdrawal is an argument against 'drug holidays'. One response is to limit the duration of relapse by detecting it sooner, in the hope that a rapid resumption of drug therapy would speed recovery. This policy would be easier to pursue with a valid and sensitive method such as the PAT.

The second type of relapse (with recovery) was extended in time, refractory to CPZ, and apparently spontaneous. It resembled the clinical phenomenon of periodic relapse and remission known to occur with some schizophrenics. Indeed, with Patient 3 the clinical ratings of thought disorder (BPRS Factor III: Guy, 1976) and Global Rating scores increased in parallel with $M_f$ during Study 1. This pattern of relapse with recovery indicates a self-limiting manifestation of schizophrenia in some patients and might denote a syndrome of schizophrenia. The underlying mechanism is particularly important to understand since it might be modifiable by future drugs.

The third type of relapse spanned two years, was unmodified by CPZ, and touched at least eight of the ten patients. It might be that these were better controlled by the neuroleptics which preceded Study 1 (c.f., Ayd, 1975; Pi and Simpson, 1981; Hollister and Kim, 1982). Such benefits, however, would have needed to exceed any effects achievable by the highest doses of CPZ in order to explain the slow relapse. Alternatively, the deterioration represented natural progression of the illness. A similar progression over three years was detected by a different objective measure of schizophrenia, based on the syntactical analysis of speech (King et al., 1990). The capacity to measure subtle trends in the progression of schizophrenia might encourage searches for underlying mechanisms and for drugs to arrest the process.

The fourth type of relapse was a labile pattern of short-period relapse and recovery, which again was resistant to neuroleptics. The pattern did not often coincide with similar periodicities in the ratings of Study 1. One cause could be error of measurement. This was low with the PAT, whereas ratings were more prone to error
owing to their poor anchorage at the 'normal' pole (Chapter IV). Other sources of variation would be life events, as when the father of Patient 14 died. However, lability intrinsic to the illness itself cannot be excluded. The amplitude of this lability was sometimes considerable. Hence drugs which might stabilize the illness would confer a real benefit.
CHAPTER VII

Study 3: Auditory Sustained Attention in Schizophrenia: A Comparison of the PAT and the CPT

1 INTRODUCTION

This small study was conducted in order to compare the PAT with the widely used and more familiar Continuous Performance Task (CPT) introduced by Rosvold et al. (1956). The comparison would determine if the PAT offers practical advantages. Also, a reservation was felt that any interpretation of PAT data might need to take account of effects resulting from the fixed subtest order and from the massed presentation of the subtests (subtests were separated by a few minutes). These methodological questions were duly explored.

The first eight patients to complete Study 2 (Chapter VI) were enrolled into Study 3 (the remaining two patients lagged too far behind in time). The methods applicable to Study 3 are described in Chapter II (Sections 1, 2, and 3.3).

2 RESULTS

2.1 Subtest Comparisons

Regression slopes of the subtest errors ($I_g$) made under diotic and dichotic conditions, at increasing rates of stimulus presentation, are shown in Figure VII.1. The figure depicts an almost linear performance trend across the three event rates which was statistically significant ($p < .001$, Friedman's two-way analysis of variance by ranks: $\chi^2 10.9$). The significance was mostly due to the high value of $I_g$ at the fast ($F1_t$) presentation rate, relative to the moderate ($M1_t$) rate ($p < .02$: Wilcoxon's matched-pairs signed-ranks test, two-tail) and slow ($S1_t$) rate ($p < .01$) which did not differ significantly from each other. The regression slope of $I_g$ under the dichotic condition was not significant, suggesting a performance ceiling at the three presentation rates.

Dichotic errors at the slow ($S2_t$) and moderate ($M2_t$) presentation rates were significantly greater than the corresponding diotic errors, $S1_t$ and $M1_t$ respectively. The present subtest M1 was equivalent to the standard auditory CPT: the subtest was administered once during the day at an event rate of one per second, and was continuous for five minutes with fifty targets to be detected. However, the CPT uses the interval to the next stimulus as its time-window for scoring omission and commission errors. Thus a late response is counted twice, both as an omission and commission error. Usually, however, only omission errors are reported. The results
Figure VII.1 Effects of event rate and diotic/dichotic stimulation on PAT performance. Closed circles = dichotic stimulation; open circles = diotic stimulation; index of errors ($I_e$) and SEM. *p < .05; **p < .02 (Wilcoxon's matched-pairs signed-ranks test, two-tail).

Presented so far used a time-window adjusted to the event rate (S1/S2 4 sec; M1/M2 2 sec; F1/F2 1.5 sec) and the error index.

With respect to the effects of diotic event rates, when subtests S1, M1 and F1 were compared, after scoring them in the customary CPT manner (Table VII.1), it was found that patients made more omission errors with M1 than S1 (p < .05: Wilcoxon's matched-pairs signed-ranks test, two-tail), and fewer with M1 than F1 (p < .01). Commission errors were higher only for M1 as compared to S1 (p < .05).

In comparisons with dichotic conditions (Table VII.1) subtest M1 caused fewer omission errors than subtests M2 and F2 (p < .01), but did not differ significantly from S2. Commission errors revealed no significant differences.

Table VII.1 Also shows that when omission and commission errors are scored relative to the current inter-stimulus interval (CPT method) the two classes of errors are significantly correlated under the diotic condition.
TABLE VII.1

Comparison of CPT and PAT
(scored according to CPT criteria: mean errors)

<table>
<thead>
<tr>
<th>Subtest</th>
<th>Omission</th>
<th>Commission</th>
<th>Correlation^1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT subtest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>8.8</td>
<td>7.8</td>
<td>.935**</td>
</tr>
<tr>
<td>Other Subtests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>4.3*</td>
<td>3.1**</td>
<td>.810*</td>
</tr>
<tr>
<td>F1</td>
<td>16.9**</td>
<td>5.9</td>
<td>.887**</td>
</tr>
<tr>
<td>S2</td>
<td>13.3</td>
<td>3.3</td>
<td>.583</td>
</tr>
<tr>
<td>M2</td>
<td>16.5**</td>
<td>7.5</td>
<td>.286</td>
</tr>
<tr>
<td>F2</td>
<td>19.9**</td>
<td>10.5</td>
<td>.268</td>
</tr>
</tbody>
</table>

^1 Statistical comparisons between M1 omission or commission errors and all other subtests, respectively (Wilcoxon's matched-pairs signed-ranks test, two-tail).

^2 Correlations between omission and commission errors (Spearman's rank correlation coefficient).

* p < .05; ** p < .01.

2.2 Subtest Order

The patients' performance on subtests S1, F1, S2, F2 when randomly ordered and given one per day is compared in Table VII.2 with that of the preceding test-occasion (two weeks earlier) when the same subtests were given in a fixed order during a single session. The patients' previous medication (300% CPZ, and orphenadrine) did not change. No statistically significant difference of any error index value was observed between the random and fixed orders of presentation (Table VII.2). In addition Figure VII.2 shows examples of the I_e values distributed across the sequential thirds of the four subtests given in the fixed order. For none of the four patients illustrated is there a consistent trend of errors across the subtests.

3 DISCUSSION

The error index analysis showed that severely ill schizophrenics found all three dichotic subtests about equally difficult. However, the nearly linear trend of performance across the three event rates under the diotic condition, exposed a residual capability that is sensitive to the rate of stimulus presentation. This confirmed also the general impression that the patients continued to direct their effort towards the task.
TABLE VII.2
Effects of subtest presentation order on PAT subtest values

<table>
<thead>
<tr>
<th>Subtest Order</th>
<th>S1</th>
<th>F1</th>
<th>S2</th>
<th>F2</th>
<th>(M_i)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random</td>
<td>0.095</td>
<td>0.327</td>
<td>0.295</td>
<td>0.343</td>
<td>0.265</td>
</tr>
<tr>
<td></td>
<td>(0.116)</td>
<td>(0.264)</td>
<td>(0.200)</td>
<td>(0.209)</td>
<td>(0.159)</td>
</tr>
<tr>
<td>Fixed</td>
<td>0.155</td>
<td>0.326</td>
<td>0.315</td>
<td>0.397</td>
<td>0.298</td>
</tr>
<tr>
<td></td>
<td>(0.224)</td>
<td>(0.165)</td>
<td>(0.262)</td>
<td>(0.170)</td>
<td>(0.191)</td>
</tr>
</tbody>
</table>

1 Wilcoxon's matched-pairs signed-ranks test (two tail): no significant differences.
2 Sequence: S1, F1, S2, and F2. Note the marked severity of illness: \(M_i\) values.

When the subtests were scored according to the CPT method (omission errors relative to the interstimulus interval) the CPT (subtest M1) differed from all other subtests except S2. Thus the CPT would be too difficult for patients able only to perform S1 and too easy for those requiring F1, or a dichotic condition, to reveal their deficit. Hence the range of disability monitored by the CPT is very limited as compared to the PAT.
Also the CPT mode of scoring confounds errors with the response latency. Late responses are counted twice i.e., as omission and commission errors. This would explain why the omission and commission errors were significantly correlated. The relationship applied only to the diotic subtests probably because dichotic responses were too few. The confounding would also explain why the performance of subtests S1 and M1 did not differ according to the index of errors yet differed significantly in terms of CPT omission and commission errors. Patients pace their response latencies to the rhythm of stimulus events (c.f., Chapter IX). With subtest S1 the two second interstimulus interval was about long enough to capture the majority of responses. With M1, however, the interval was often too short and late responses more often masqueraded as omission errors. This explanation is confirmed by the significantly more frequent M1 than S1 commission errors. A similar situation did not arise with the F1 subtest because some patients made too few responses for any to fall outside the interstimulus interval hence the variance was increased.6

The observed correlation of omission and commission errors (CPT mode of scoring) with the diotic subtests and not the dichotic subtests suggests that the patients 'gave up' i.e., abandoned the response set and so failed to maintain attention, as the task became more difficult. Their omitted responses were genuine rather than simply late as in the diotic case. This supports the argument to be presented in Chapter X that attention is a resource deployed by behavioural plans. Sustained attention fails when the prevailing plan is replaced by a competing option.

It may be concluded that the event rate used most widely with the CPT (1/sec) is the worst of all evils given the scoring method. Moreover, because response latencies or reaction times are generally insensitive to neuroleptics in schizophrenia (Chapters X; reviews: Nuechterlein, 1977; Mannuzza, 1980; Cassens et al., 1990), the confounding of latency with errors further reduces the sensitivity of the CPT to neuroleptic effects. This situation does not arise with the PAT which provides adequate response windows and uses the error index to correct omission errors for the commission error rate (Pigache, 1976).

The PAT includes two subtests (F1 and F2) which are more difficult to perform than the auditory CPT (M1). In its turn the auditory CPT is more difficult than its visual equivalent (Sykes et al., 1972; Mussgay and Hertwig, 1990). Hence it is not altogether surprising that the F2 subtest of the PAT was sensitive to the effects of nitrous oxide inhalation by healthy volunteers, whereas the visual CPT was

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6 Patients less severely ill than the present sample perform F1 rather well, but may have difficulties with F2. In their case the interstimulus interval of 0.5 sec with F1 and F2 would be even more sensitive to late responding if scored by the CPT method.
not (Fried et al., 1994).\(^7\) Beatty (1982) reported that auditory detection tasks impose a higher processing load and are more difficult for healthy subjects than similar visual tasks.

In addition various findings suggest that the auditory modality may be particularly susceptible to defective information processing in schizophrenia. This was noted by Giora (1975) with respect to retarded reaction times and the modality shift effect; by Duncan (1988) who obtained smaller auditory than visual P300 amplitudes from schizophrenics, but not from healthy subjects; and by Mussgay and Hertwig (1990) who found that schizophrenics were more impaired by an auditory than visual CPT, whereas healthy subjects and alcoholics were not.

The visual CPT is almost the only version in current use although its efficiency lies below that of the auditory CPT (Ml). Most probably it is often too easy for schizophrenics except the most severely ill. This would explain why in the literature the visual CPT often fails to yield clinical correlations or neuroleptic effects. Yet in so far as the visual CPT relies upon the cooperation of the subject, who must orient his gaze and focus in order to encode the stimuli, it also may demand too much of severely ill patients. Hence the PAT seems to provide a more appropriate range of difficulty than does the CPT for schizophrenics with diverse degrees of illness. Also PAT stimuli are heard without special effort.

Although the CPT has long been held (Mirsky and Kornetsky, 1964) to measure sustained attention (its AX versions add a memory component) it is now apparent that the CPT measures, too, slowness of response and confounds the two variables. Many versions of the CPT add a memory component in order to increase the processing demands (Wohlberg and Kornetsky, 1973; Comblatt and Erlenmeyer-Kimling, 1985; Buchsbaum et al., 1985; Comblatt et al., 1988; Earle-Boyer et al., 1991). However, all retain the event rate of 1/sec and limit correct responses to the interstimulus interval. By contrast the PAT monitors sustained attention (with no memory load) independently of the response latency (Pigache, 1993a & Chapter IV). The PAT also measures other separable aspects of attention.

This study further demonstrated that the fixed order of subtests used throughout this thesis did not account for the PAT findings. Although the number of patients in the present study was small the statistical power was quite sufficient to demonstrate numerous significant differences of performance. Hence any effect of subtest order or of massed presentation was probably negligible. Similarly, no order effect was observed between successive versions of the CPT (Mussgay and Hertwig, 1990).

CHAPTER VIII

Different Patterns of Auditory Attention (PAT) Performance
Discriminate between Healthy Subjects and
Chronic Schizophrenics

1 INTRODUCTION

Up to this point schizophrenics only have been considered. However, it is important to know whether or not the PAT can discriminate between schizophrenic and healthy subjects. Such a result would be expected since a corresponding difference was shown for the Continuous Performance Test (Orzack and Kornetsky, 1966; Wohlberg and Kornetsky, 1973; Asarnow and MacCrimmon, 1978). This chapter describes the results for the PAT and explores how schizophrenics differed from healthy subjects in terms of the selective attention, slow processing, and sustained attention hypotheses.

Chapman and Chapman (1977 and 1978) argued that in order to demonstrate a true qualitative difference between schizophrenics and healthy subjects it is necessary to match the groups on other tests. Such a match would eliminate the possibilities of a 'generalized performance deficit' and of similarities resulting from 'floor' or 'ceiling' effects. Suppose, however, that the defect in question is so basic that its effects are pervasive? All tests might be affected and a match would not then be possible. Or, suppose that the defect can be normalized by neuroleptic drugs? A group difference might disappear if the match were achieved by selecting treated patients responding to the therapy.

The strategy adopted here was first to compare a group of schizophrenics (receiving chlorpromazine) with healthy subjects in order to demonstrate performance differences. Then a subgroup of treated patients was identified which apparently performed like the healthy subjects. Placebo was substituted for chlorpromazine (all patients) and the schizophrenic subgroup was again compared to the healthy subjects. Any recrudescence of the deficit would suggest a functional origin; and not an irreversible global processing defect, or a basis in structural neuropathology. The methods are described in Chapter II (Sections 1, 2, and 3.4).

2 RESULTS
2.1 Mean \( I_E \)

Distributions of the \( Ml_E \) values of schizophrenics and healthy subjects are depicted in Figure VIII.1 and compared in Table VIII.1. The range of schizophrenic values was much wider than that of the healthy subjects (a log scale was used to
reduce the figure size). Thus a subgroup of thirteen schizophrenics (open circles) was identified with $M_E$ values < 0.1 which also lay within the healthy range.

**Figure VIII.1** Distributions of Mean $I_E$ values of schizophrenics and healthy subjects. Mean $I_E$ values of the twenty schizophrenics (open symbols) are drawn as circles for 13 patients with $M_E$ values < 0.1 and lying within the range of healthy subjects; and as squares for 7 patients with more extreme values. The $M_E$ values of 11 healthy subjects are depicted as solid circles.
The $M_I$ values of the twenty schizophrenic patients were significantly higher than those of the healthy subjects (Table VIII.1). The difference occurred despite the stabilized CPZ treatment of the schizophrenics. There was no such difference, however, for the subgroup of thirteen schizophrenics receiving CPZ. This result was changed by substituting placebo for CPZ. The $M_I$ values of all patients increased significantly after placebo, with respect to performance on the first test-occasion (Wilcoxon's signed-ranks matched-pairs test, two-tail: $p < .01$, $n=20$ and $n=13$ patients). As a consequence the $M_I$ values of the thirteen schizophrenics increased significantly relative to those of healthy subjects, after placebo was substituted for CPZ (Table VIII.1). This was also true for all twenty patients (data not shown).

### TABLE VIII.1

Comparison of schizophrenic and healthy subjects in terms of PAT subtest $I_E$ values (SD)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>S1 $I_E$</th>
<th>F1 $I_E$</th>
<th>S2 $I_E$</th>
<th>F2 $I_E$</th>
<th>M $I_E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy n=11</td>
<td>0.007</td>
<td>0.016</td>
<td>0.020</td>
<td>0.057</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>(0.010)</td>
<td>(0.023)</td>
<td>(0.030)</td>
<td>(0.053)</td>
<td>(0.026)</td>
</tr>
<tr>
<td>Schizophrenic CPZ</td>
<td>0.019</td>
<td>0.100</td>
<td>0.140***</td>
<td>0.240**</td>
<td>0.121***</td>
</tr>
<tr>
<td>n=20</td>
<td>(0.033)</td>
<td>(0.121)</td>
<td>(0.234)</td>
<td>(0.255)</td>
<td>(0.130)</td>
</tr>
<tr>
<td>Schizophrenic CPZ</td>
<td>0.002</td>
<td>0.031</td>
<td>0.045</td>
<td>0.098</td>
<td>0.046</td>
</tr>
<tr>
<td>n=13</td>
<td>(0.005)</td>
<td>(0.050)</td>
<td>(0.054)</td>
<td>(0.066)</td>
<td>(0.026)</td>
</tr>
<tr>
<td>Schizophrenic</td>
<td>0.137***</td>
<td>0.217***</td>
<td>0.338***</td>
<td>0.445***</td>
<td>0.285***</td>
</tr>
<tr>
<td>Placebo n=13</td>
<td>(0.217)</td>
<td>(0.245)</td>
<td>(0.355)</td>
<td>(0.304)</td>
<td>(0.257)</td>
</tr>
</tbody>
</table>

Mann-Whitney U-test (two-tail) patients versus healthy subjects: ** $p < .01$; *** $p < .005$.

1 All 20 patients first test-occasion, previous neuroleptics replaced by CPZ (300-900 mg/day) for 3 to 9 months.
2 Subgroup of thirteen patients ($M_I < 0.1$).
3 Same thirteen patients, as above, but after nine weeks of placebo.

### 2.2 Subtest $I_E$ Values

The dichotic subtest F2 and S2 $I_E$ values of the twenty schizophrenic patients under CPZ treatment were significantly higher than those of the healthy subjects (Table VIII.1). This was not the case for the subgroup of thirteen patients. However, after placebo substitution the $I_E$ values of all four subtests increased significantly as compared to the CPZ treatment (Wilcoxon's signed-ranks matched-pairs test, two-tail: $p < .01$, $n=20$ and $n=13$ patients). As a result all subtest $I_E$ values increased
significantly for the subgroup (Table VIII.1) relative to those of healthy subjects; and for all twenty patients (data not shown).

2.3 Raw Error Scores

The raw omission and commission errors of all subtests were pooled for all subtests (Table VIII.2). The twenty schizophrenics and the subgroup of 13 patients made significantly more errors of omission than did the healthy subjects. Commission errors did not increase significantly, but the ratio of commission to omission errors was higher for healthy subjects.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Errors ( \Sigma ) all subtests (SD)</th>
<th>Omission</th>
<th>Commission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy ( n=11 )</td>
<td>3.5 ( (4.03) )</td>
<td>3.2 ( (4.51) )</td>
<td></td>
</tr>
<tr>
<td>Schizophrenic ( CPZ n=20^1 )</td>
<td>20.6*** ( (21.58) )</td>
<td>7.4(^\dagger) ( (10.28) )</td>
<td></td>
</tr>
<tr>
<td>Schizophrenic ( CPZ n=13^2 )</td>
<td>7.4** ( (4.09) )</td>
<td>3.8 ( (2.92) )</td>
<td></td>
</tr>
</tbody>
</table>

Mann-Whitney U-test (two-tail) patients versus healthy subjects: *** \( p < .001 \); ** \( p < .01 \); \(^\dagger\) \( p = .056 \).

1 All 20 patients, first test-occasion, previous neuroleptics replaced by CPZ (300-900 mg/day) for 3 to 9 months.
2 Subgroup of thirteen patients \( (M_{1g} < 0.1) \).

2.4 Selective Attention

The data of Table VIII.1 were used to evaluate the effects of dichotic versus diotic stimulation (Wilcoxon's signed-ranks matched-pairs test, two-tail). Healthy subjects made significantly more dichotic than diotic errors at the fast presentation rate only (F2 vs. F1: \( p < .01 \)). Schizophrenics (both populations) made significantly more dichotic than diotic errors at either presentation rate (F2 vs. F1 and S2 vs. S1: \( p < .01 \)).

2.5 Information Processing Rate

The data of Table VIII.1 were also used to evaluate the effects of fast versus slow event rates, stimulation (Wilcoxon's signed-ranks matched-pairs test; two-tail).
Healthy subjects made significantly more errors at the fast presentation rate under the dichotic condition only (F2 vs. S2: p < .01). Schizophrenics (both populations) made significantly more fast processing errors under both diotic (F1 vs. S1: n=20, p < .01; n=13, p < .05) and dichotic (F2 vs. S2: n=20, p < .05; n=13, p < .01) conditions.

**Figure VIII.2** Distributions of percent $l_e$ over subtest thirds for schizophrenic and healthy subjects. The "seven-field algorithm partitioning a triangular surface" was applied to the thirds of each subtest for each subject to classify the profile of $l_e$ values. The large triangle is a graph showing the percentage of total errors ($l_e$) in the last third of a subtest (ordinate) plotted against those in the second third (abscissa). The temporal profiles of all twenty schizophrenics for the four subtests are represented by open symbols: circles for the 13 patients with $M_{l_e}$ values < 0.1 in Figure VIII.1; squares for the 7 patients with more extreme $M_{l_e}$ values. The temporal profiles of ten healthy subjects (the eleventh made no errors on any subtest) are represented by solid circles. The boundaries of the seven fields are indicated by dashed lines. The intermediate triangle shows the field boundaries and the average field trends, each representing all possible error profiles (%) within a particular field. The small triangle (top right corner) depicts how the fields were numbered, from top to bottom, and from right to left for convenience. It may seen in the large triangle that the schizophrenics cluster in fields 1, 2 and 3, with data from the seven most severe patients (open squares) predominant centrally. The highest concentration of data from healthy subjects lies in field 7.
2.6 Sustained Attention

A scatter plot of the $I_E$ distribution over the successive thirds of all subtests (combined) for the schizophrenic and healthy subjects is shown in Figure VIII.2. The thirds are represented two-dimensionally by the surface of the triangle in the figure. Within the triangle each point represents a unique profile of percent errors, i.e., a distribution over the sequential thirds of a subtest. At the origin of the graph (Figure VIII.2) the last two-thirds of a subtest account for 0% of total errors, and the first one-third accounts for 100% of the total. Conversely, the first one-third accounts for 0% of the total at all points along the hypoteneuse, and *either* one of the last two-thirds for 100%. Also, each point can accumulate data from more than one individual. Each field within the triangle is characterized by an average trend (pattern) that is not an average of the data. The data (%) are replaced by the field trends and quantified as field frequencies.

A frequency analysis of the most prevalent fields (patterns) is shown in Table VIII.3. The frequencies of temporal patterns 1 + 2 + 3 were pooled to form a sequence representing progressive temporal impairment (time-on-subtest decrement). The schizophrenics (both populations) distributed their errors according to thirds patterns significantly more often than did the healthy subjects. By contrast, the healthy 1 + 2 + 3 subjects made significantly more frequent first third errors (Thirds Pattern 7). Errors in the remaining thirds and error-free subtests (not presented) brought the various group totals of Table VIII.3 to 100%.

**TABLE VIII.3**

Comparison of schizophrenic and healthy subjects in terms of subtest thirds error patterns

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sustained Attention</th>
<th>First Third</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patterns 1 + 2 + 3</td>
<td>Pattern 7</td>
</tr>
<tr>
<td></td>
<td>% Subtests</td>
<td>% Subtests</td>
</tr>
<tr>
<td>Healthy</td>
<td>13.6</td>
<td>22.7</td>
</tr>
<tr>
<td>n=11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenic</td>
<td>50.0</td>
<td>7.5</td>
</tr>
<tr>
<td>CPZ n=20$^1$</td>
<td>(p &lt;.003)</td>
<td>(p &lt;.001)</td>
</tr>
<tr>
<td>Schizophrenic</td>
<td>34.6</td>
<td>5.8</td>
</tr>
<tr>
<td>CPZ n=13$^2$</td>
<td>(p &lt;.05)</td>
<td>(p =.059)</td>
</tr>
</tbody>
</table>

Mann-Whitney U-test (two-tail) patients versus healthy subjects.

1 All 20 patients, first test-occasion, previous neuroleptics replaced by CPZ (300-900 mg/day) for 3 to 9 months.
2 Subgroup of thirteen patients ($M_E < 0.1$).
3 DISCUSSION

In terms of $M_6^g$ the 'matched' subgroup of thirteen patients, when treated with CPZ, performed the PAT much as did healthy subjects. In this respect they did not exhibit a global processing defect. All subjects in this study cooperated fully. Since the patients were generally less well educated than the healthy subjects this variable, too, would not explain the findings. Also, no correlation was obtained previously between PAT performance and IQ scores, and no practice effect was found (Chapter IV).

Conversely the 'matched' schizophrenics on CPZ made more omission errors than did the healthy subjects, and were less able to sustain attention throughout the subtests. Accordingly these findings do suggest a persistent pathological process.

It should be noted that the more frequent omissions made by the schizophrenics was consistent with their higher error index scores. However, the omission errors were pooled from all four subtests thus summing small increases. Whereas the index was calculated for each subtest separately.

The relative difficulty of the individual subtests was different for the two groups. For the healthy subjects F2 was the only subtest to be significantly more 'difficult' than any other. By contrast the schizophrenics (either population receiving CPZ) made significantly more dichotic than diotic errors at both presentation rates, and significantly more fast processing errors under both listening conditions. Hence a processing problem remained for the 'matched' subgroup of schizophrenics. This was not caused by the therapy since the deficits worsened when placebo was substituted for CPZ. The impairments were attenuated by CPZ.

The observation that schizophrenics made more dichotic than diotic errors might suggest impaired selective attention. However, the lack of any significant increase of commission errors did not indicate a high rate of responding to non-target stimuli. Also, the dichotic performance of the schizophrenic subgroup (when receiving CPZ) did not differ significantly from that of the healthy subjects. Thus dichotic distraction did not markedly impair these patients.

It still remains possible that selective attention was seriously impaired for the present schizophrenics. Although the dichotic material failed to elicit the deficit other distractors with greater subjective relevance, lying outside the task, might have subverted attention (c.f., Schneider, 1976). Such extraneous distraction would have been manifest as impaired sustained attention relative to the PAT. Every precaution was taken to minimize obvious external distractions, but the patients' thoughts were their own. However, one would expect distracting thoughts to 'pop into the head' at random throughout a subtest. Instead, the results showed a temporal performance
decrement necessitating a tempoally congruent distribution of internal distractors. Hence the present findings are not explained simply by impaired selective attention.

The higher errors by schizophrenics on the fast subtests relative to the slow might suggest slowed information processing. However, the performance of the schizophrenic subgroup (when receiving CPZ) on the fast subtests did not differ significantly from that of the healthy group. Thus fast stimulation, too, did not markedly impair the schizophrenic subgroup.

Sustained attention problems (Patterns 1 + 2 + 3) were slight for the healthy subjects. Instead, their relatively frequent distribution of errors as Pattern 7 suggests initial incertitude about the response set, perhaps because they were not given a preliminary familiarization trial with the PAT.

By contrast, the capacity to sustain attention for five minutes was noticeably impaired amongst the schizophrenics despite neuroleptic treatment. This was true even for the subgroup of thirteen patients which otherwise demonstrated no major deficit with dichotic or fast stimulation, as compared to the healthy group. Hence the problematic aspect of the PAT for schizophrenics seems not related to the burden put on sustained attention. Similar effects of the information processing-load have been described for complex versions of the CPT used in schizophrenia (Earle-Boyer et al., 1991; Nuechterlein et al., 1986; Comblatt et al., 1988; Comblatt, Lezenweger and Erlenmeyer-Kimling, 1989). Why this might be so is discussed in Chapter XI.

The interaction of impaired sustained attention with the dichotic and fast modes of stimulus presentation may be explained as follows. The range of PAT subtests offers worsening 'cost/benefit' ratios to the subject, because a higher density of attention (observing responses) is required by both the dichotic and fast modes of presentation. The fast presentations quadruple the stimulus rate, as compared to the slow subtests, and so require a commensurate increase in the rate of emitting observing responses ('cost') (Jerison and Pickett, 1964). Hence a time-pressure to respond is crucially important (Harwood and Naylor, 1963). The dichotic presentations double the rate of ostensible 'targets' (as compared to the diotic subtests) and reduce the signal-to-noise ratio by delivering distraction to one ear; thus longer applications of attention are needed for all decisions (more 'cost'). Nonetheless the more 'difficult' PAT subtests offer no more incentive than do their 'easier' counterparts ('benefit': 50 targets to be 'hit'). Hence for all subjects the fast dichotic subtest (F2) suffered the most from inadequate attention. The sustained attention deficit of the schizophrenics was aggravated by both fast and dichotic subtests.

Schizophrenics attended less well than healthy subjects during a relatively undemanding experimental task (PAT). It may be that autonomous distraction was
more abundant and more potent for the patients than for healthy subjects. Alternatively, the patients were possibly less successful at maintaining their behavioural set in the face of distractors. It is the Author's belief, supported by the literature, that schizophrenia leads to the first situation (distraction) whereas neuroleptics improve the second (set maintainance).
CHAPTER IX

Attention Defects in Schizophrenia

1 INTRODUCTION

Performance of the PAT was previously shown (Chapters IV, V, VI and VIII) to provide a clinically relevant measure of schizophrenia. Since the task measures aspects of attention and no equivalent alternative exists (Chapter VII) it becomes important to understand fully what the PAT measures in schizophrenia. In Chapter VIII it was found that schizophrenics treated with CPZ or receiving placebo were relatively more impaired by dichotic stimulation or fast event rates than healthy subjects; but this was not sufficient to account for the patients' overall worse performance which differed mainly in terms of poor sustained attention.

The latter study, however, was unable to identify how selective attention and processing speed interacted with sustained attention. The question was addressed by the study reported in Chapter IV which was then only partially analyzed. That study explored the relationship between the three parameters as performance changed with the severity of schizophrenia. The results of the remaining analyses (planned a priori) are now reported. The findings relate not only to schizophrenia but bear upon the broader concept of attention itself.

The selective attention hypothesis was tested first in terms of PAT intrusion errors during the dichotic subtests. Dichotic listening tasks (different messages delivered to the two ears) comprise a well established paradigm for testing selective attention, where the message to one ear must be ignored (Broadbent, 1952; Cherry, 1953; Moray, 1969; Triesman, 1964). The literature is divided as to whether schizophrenics do make more intrusion errors than control groups on such tasks (Hawks & Robinson, 1971; Dykes & McGhie, 1976; Wahl, 1976) or do not (Wishner & Wahl, 1974; Payne, Hochberg and Hawks, 1970; Schneider, 1976; Straube & Germer, 1979; Allen, 1982). The hypothesis was also tested by relating the $I_g$ values of diotic and dichotic subtests to the severity of illness as indexed by $MI_g$ (Chapters IV & V).

The rate of information processing was measured as the latency of correct responses, and as the $I_g$ values of slow and fast subtests, related to the severity of illness ($MI_g$).

Sustained attention can fail either as a function of time-on-task or intermittently. Both forms of deficit were analysed in relation to the distribution of errors over the successive thirds of each PAT subtest, according to the algorithm of Chapter III, and with respect to the severity of illness ($MI_g$).
Details of the methods are described in Chapter II (Sections 1, 2, 3.1.1 to 3.1.4, 3.1.8 and 3.4.4).

2 RESULTS

2.1 Selective attention

The strongest evidence for a failure of selective attention would be a preponderance of commission errors indicating distractibility, rather than omission errors, especially if the errors were made to dichotic 'wrong-ear targets' (intrusion errors). However, it is evident from Figure IX.1 that omission errors predominated. One might still be persuaded that distraction contributed an important effect if the majority of dichotic commission errors were made to 'wrong-ear targets'. This, too, was not the case. Despite this it would seem that most commission errors (to non-targets in either ear or to 'wrong-ear targets') were made during the dichotic subtests (Figure IX.1). However, the errors to non-targets were almost equally frequent under both diotic and dichotic conditions. Nonetheless, there was some evidence of increased distractibility for some patients. Ten patients increased their commission errors towards the end of the placebo period (Figure IX.1).

A less specific indication of a performance deficit associated with the dichotic subtests was provided by the error index (which combines omission and commission errors). The dichotic subtests F2 and S2 yielded significantly higher $I_E$ values (Figure IX.2) at all levels of impairment ($M_{12}$) than did F1 and S1, respectively (Wilcoxon's matched-pairs signed-ranks test, two-tail: $p < .01$). The same was true for the corresponding grand means of all test-occasions (Table IX.1).

### TABLE IX.1

<table>
<thead>
<tr>
<th>Subtest $I_E$ Values (SD)</th>
<th>S1 $I_E$</th>
<th>F1 $I_E$</th>
<th>S2 $I_E$</th>
<th>F2 $I_E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0.181)</td>
<td>(0.211)</td>
<td>(0.246)</td>
<td>(0.248)</td>
<td></td>
</tr>
<tr>
<td>Fast v Slow</td>
<td>p &lt; .01</td>
<td>p &lt; .01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diotic</td>
<td>p &lt; .01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>v</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dichotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$ Wilcoxon's matched-pairs signed-ranks test, two-tail.
PAT omission and commission errors. Omission and commission errors of all four subtests were combined for test-occasions representing equivalent treatment sequences in the two halves of the cross-over design. Patients were sorted into four homogenous groups according to their patterns of error distribution. Ten patients made frequent omission and commission errors with both types of error increasing under placebo; one patient caused the sharp increase of commission errors on the first test-occasion under 50% dose CPZ (his father had died the previous day). Three patients made frequent omission errors which increased under placebo, and almost no commission errors. Two patients made abundant omission errors which increased under placebo, and frequent commission errors. Five patients made few errors of either kind with little change under placebo. The maximum number of targets was 200. Commission error subtypes: black segments = 'wrong-ear' targets; hatched segments = other 'wrong-ear' errors; open segments = 'correct ear' errors.
Lastly the error difference ($I_E$) between the diotic and dichotic subtests (dichotic error increment, based upon the grand means of all test-occasions), expressed as a percentage of all subtest $I_E$ values, declined exponentially (Figure IX.3) with more severe illness, as measured by $M_{I_E}$ (Spearman's rank correlation coefficient: $r_s = 0.747$, $p < .01$). Thus the $I_E$ difference (percent) between the dichotic and diotic subtests reached a nadir as PAT performance continued to deteriorate. Hence dichotic errors ($I_E$) accounted only partially for the overall impairment.

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$\text{Percent dichotic increment} = \frac{(F2I_E + S2I_E) - (F1I_E + S1I_E) \times 100}{S1I_E + F1I_E + S2I_E + F2I_E}$
2.2 Information processing rate

The PAT measures the latencies of correct responses, but confounds the decision and response components. With this proviso response latencies can be related to the severity of illness measured by the error index. It is evident from Figure IX.4 that the response latencies of both S1 and F1 were significantly correlated to their respective $I_E$ values (Spearman's rank correlation coefficient: S1 $r_s 0.47$, $p < .05$; F1 $r_s 0.78$, $p < .001$). However, with more severely ill patients ($I_E$ values high) the latencies of both subtests increased equally (parallel slopes). The response latencies under F1 were significantly faster than under S1 (Wilcoxon's matched-pairs signed-ranks test, two-tail: $p < .001$). This difference was not affected by the substitution of placebo for CPZ.

Because the slopes of Figure IX.4 are parallel the response latencies of the two subtests were summarized by their mean. Plots of the mean RL values indicated that for seven cases (Patients: 1, 3, 10, 11, 12, 16, and 17) mean RL was related to two independent measures of clinical state namely the Global Rating score and $M/L_E$. The relationships shown in Figure IX.5 for Patients 3 and 16 comprised trends rather than point-to-point correspondences, but are remarkably congruent. There were no
significant correlations between mean RL and years of chronicity ($r = 0.27$), years of institutionalization ($r = 0.29$), or age ($r = 0.26$).

The effect of event rate upon performance was estimated, too, by comparing errors ($I_E$ values) for the slow ($S_1 + S_2$) and fast ($F_1 + F_2$) subtests at increasing levels of $M_I_E$ (Figure IX.2). This showed that $F_1I_E$ values at all levels of $M_I_E$ were significantly higher than $S_1I_E$ (Wilcoxon's matched-pairs signed-ranks test, two-tail: $p < .01$); and $F_2I_E$ values were higher than $S_2I_E$, except at $M_I_E$ 0.5. The same held true for the corresponding grand means of all test-occasions (Table IX.1).

The error difference ($I_E$) between the fast and slow subtests (fast error increment, based upon the grand means of all test-occasions), expressed as a percentage of all subtest $I_E$ values, was unrelated to the severity of illness as measured by $M_I_E$ (Spearman's rank correlation coefficient: $r = 0.015$). The relatively constant proportion of $I_E$ (average 18.7%) indicates that slow information processing was not a major cause of deteriorating PAT performance.

2.3 Sustained attention

When all subtests were combined the $I_E$ values of the last two thirds were found to be significantly higher than those of the first one-third (Figure IX.6) at all levels of impairment ($M_I_E$). This temporal decrement of performance indicated a progressive loss of sustained attention over the five minutes of a subtest.

On each test-occasion the pattern of successive thirds of each subtest was classified according to the seven-field algorithm (Chapter III) preliminary to examining how $I_E$ values were distributed as temporal patterns (Figure IX.7). When all 112 subtests (4 subtests x 28 test-occasions) per patient were considered, zero errors were made on 20.6 (average) of this total and most $I_E$ values were low; the temporal $I_E$ patterns were distributed as shown in Figure IX.7. The frequencies of all patterns except Pattern 3 (P3) were highest at low $I_E$ values (especially for bin $I_E$ 0.1). Temporal patterns P1 to P3 were the most abundant. The impression that a constant proportion of errors was distributed as P3, up to $I_E$ 1.0 (for most cases indicating the maximum omission score) in Figure IX.7, is misleading since it simply reflected the diminishing number of subtests with high $I_E$ values. When the percentage contribution of each temporal pattern to each level of $I_E$ was considered the result was different.

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9 Percent dichotic increment = \[ \frac{(F2I_E + F1I_E) - (S2I_E + S1I_E)}{S1I_E + F1I_E + S2I_E + F2I_E} \] x 100
10 Temporal increment = \[ \frac{(II_E + III_E) - (2 \times I_E)}{II_E + III_E + II_E} \]
Figure IX.4  PAT response latencies. Correlations between response latencies (RL) and $I_E$ values for the slow (S1) and fast (F1) diotic subtests. Each point is the average of about one-thousand measurements, but the RL data of Patients 4 and 20 were never scored.
FIGURE IX.5  Response latencies and severity of schizophrenia (MfG). Data are from two patients who showed a direct relationship between three independent variables: response latencies (RL), global rating scores, and MfG. Note the log scale for RL.
Figure IX.6  $I_E$ increments across subtest thirds and severity of schizophrenia ($M4$). Histograms of the successive thirds of all PAT subtests in bins corresponding to four levels of $M4 \pm 20\%$. Data are from all patients with $M4$ values falling within any particular bin. ** $p < .01$ (Wilcoxon's matched-pairs signed-ranks test, two-tail).

(Figure IX.8). Initially P1 predominated, but as the patients deteriorated this pattern yielded first to P2; then both these patterns, and all others, were replaced by P3. Note that at low levels of $I_E$ P3 was more frequent than required to achieve the $I_E$ values concerned ($\leq 0.5$). The major involvement of patterns P1 to P3 (Figures IX.7 and IX.8) supports the temporal decrement hypothesis.

With the analysis, above, all four subtests were combined, hence it is uncertain how far the relationships observed represented each subtest. In order to examine this matter the frequency of each subtest contributing to each temporal $I_E$ pattern was counted (Figure IX.9). It can be seen that the only significant trends were those for
Figure IX.7 Sustained attention error patterns and severity of schizophrenia (I_E). Patterns of subtest I_E thirds over all four PAT subtests were classified according to the seven-field algorithm (Chapter III); then the frequency of successive I_E bins within each temporal pattern was counted, expressed as a percentage of all test-occasions, and averaged over the twenty patients. Calculated per pattern and I_E bin as: number subtests (among 28 test-occasions x 4 subtests) containing errors / 28 test occasions x 4 subtests, per cent. All 7 distribution tails continued to diminish and are truncated. ** p < .01; *** p < .001 (Friedman's two-way analysis of variance, two-tail).

Pattern 3 and zero errors (p < .001). The Pattern 3 frequency increased as a function of subtests in the order: S1, F1, S2, F2, and the frequency of zero errors decreased complementarily. This order of subtests for P3 corresponds to the sequence of subtest 'difficulty' depicted in Figure IX.2.

The overall results suggest an interaction between manoeuvres which increase subtest difficulty (dichotic versus diotic conditions, fast versus slow presentation rates) and the sustained attention impairment. This possibility was confirmed by the data of Figure IX.10 representing the grand means of all twenty patients. It is evident that
Figure IX.8  Frequency (%) of sustained attention error patterns and severity of schizophrenia ($I_E$). Percent of all subtests and test-occasions (when patients made errors) per $I_E$ bin for the 7 patterns of $I_E$ distributed over the subtest thirds. Note the predominance of Patterns 1, 5 and 7 at $I_E$ 0.1, the emergence of Patterns 2 and 3 at $I_E$ 0.3, and the eventual dominance of Pattern 3 after $I_E$ 0.7. For all bins $p < .001$ (Friedman's two-way analysis of variance, two-tail).
Figure IX.9 Frequency (%) of sustained attention error patterns per PAT subtest. Patterns of subtest for thirds for each PAT subtests were classified according to the seven-field algorithm (Chapter III); then the frequency of subtest within each temporal pattern was counted, expressed as a percentage of all test-occasions, and averaged over the twenty patients. The frequency of zero errors was also included to account for all the data. *** p < .001 (Friedman's two-way analysis of variance, two-tail).
**FIGURE IX.10**  
$I_e$ values (grand means) across successive thirds of each PAT subtest at four severity levels ($M_I$) of schizophrenia. Four blocks of twelve cells at four levels of $M_I + 20\%$ are shown with each block representing the successive thirds four subtests. Data are from all patients whose $M_I$ values matched the blocks. Each dot represents an average increment of $I_e 0.01$.

$I_e$ values increased progressively at all levels of illness severity ($M_I$) as a function of increasing task difficulty (S1 to F2), but also with the successive temporal thirds. Thus the $I_e$ values in Figure IX.10 appear to invade the surface of each block of twelve cells from its top right-hand corner. This suggests that sustained attention became more effortful as the task difficulty increased, causing errors to encroach upon progressively earlier thirds of the subtests.

3 **DISCUSSION**

The proposition that defective selective attention is the primary cause of schizophrenia would appear to be unsupported. Distractors delivered to the ‘wrong ear’ of the dichotic subtests elicited an insufficient number of commission errors to
explain the overall poor performance. Some patients did make more commission errors towards the end of the placebo period, but the overall effect was not significant (Chapter IV). In general, when patients responded they focused attention upon the correct targets.

This conclusion is not contradicted by the greater $I_e$ values for dichotic as compared to diotic subtests. The error index is not sufficiently specific in this case because it combines commission and omission errors. Errors of either type may result from target uncertainty (reduced signal-to-noise ratio) made likely by the brevity of the digits and their erasure by succeeding digits. This uncertainty would have been increased by interference from the dichotic stimulation. The observed commission error rate suggests that when patients attended they applied a relatively relaxed criterion for target recognition under both diotic and dichotic conditions. The adopted criterion was opposite to that which would explain the observed omission error rate viz. patients then applied a strict target criterion. The foregoing conflict is resolved by assuming that the criterion was relaxed during periods of attention, but that attention was frequently withdrawn from the S2 and F2 subtests, thus resulting in omission errors. Indeed the $I_e$ difference (percent) between the dichotic and diotic subtests reached a nadir as patients continued to deteriorate. Their possible problems with selective attention lay beyond the task.

The proposition that slow information processing is the primary cause of schizophrenia was also not supported. Longer response latencies to both S1 and F1 targets were noted for a few patients as the severity of illness increased. Similar significant relationships were observed for all patients when all data were averaged, but the response latencies changed little when placebo was substituted for CPZ (Chapter IV). The inadequacy of response latency as a measure of schizophrenic deterioration, as compared to the error index, might be due to variability and few latencies as the frequency of omission errors increased.

Response latencies under F1 were significantly faster than under S1 and exceeded the 0.5 s interstimulus interval on numerous test-occasions. The S1 interstimulus of 2.0 s was exceeded on only 1.4% of test-occasions. These observations bear upon the importance of adopting suitable time-windows when scoring the errors of successive discrimination tasks (a procedure not adopted with the Continuous Performance Test: Chapter VII). The PAT time-windows made response latencies independent of the concomitant error scores (Chapter IV). The present results also showed no significant correlations between mean RL and years of chronicity, years of institutionalization, or age.
The fast stimulus rate provoked greater \( I_e \) values than did the slow. However, the omission errors incorporated in \( I_e \) cannot relate to slow responding. The interpretation is therefore similar to that for the dichotic/diotic situation. Target uncertainty as before would have been greater at the fast presentation rate when crisp speech made the digits even shorter. Although omission and commission errors were not separately analyzed with respect to the fast and slow subtests, it is again assumed that the target criterion was relatively relaxed during periods of attention, and that attention was frequently withdrawn or diverted from the F1 and F2 subtests, resulting in omission errors.

The longer response latencies, above, as patients deteriorated might also have reflected increasing uncertainty about targets. Thus whenever attention returned to the PAT after an absence the loss of set might have curtailed stimulus sampling, producing greater uncertainty and longer latencies for the next few stimuli (c.f., Posner, et al., 1980).

As patients became more ill they responded to targets slightly more slowly. However, the relatively constant \( I_e \) difference (only 18.7%) between the fast and slow subtests at all levels of illness, points to a problem more fundamental than slow information processing for these patients.

The proposition, that impaired sustained attention is the primary cause of schizophrenia, received *prima facie* support. However, it will be argued later that defective attention is a secondary manifestation of the syndrome. Although omission and commission errors were not analyzed separately with respect to sustained attention, it is evident from Figure IX.1 that omission errors predominated. Thus the increase of errors \( I_e \) values that occurred as a function of time (within five minutes) confirms that patients paid diminishing attention to the PAT.

The between-subject demonstration of a time-on-task decrement of sustained attention supported similar within-subject findings based upon the algorithm. Temporal patterns P1, P2 and P3 identified by the algorithm were the most prevalent. Moreover, as \( I_e \) values increased P1 was replaced by P2, and both patterns by P3, in an orderly manner which indicated that the ability to maintain attention persisted for ever shorter periods as the patients deteriorated. However, even at the lowest level of overall impairment 5.5% of all subtest errors were distributed as Pattern 3, a proportion that rapidly increased to 22.3% and more. Pattern 3 was not observed with healthy subjects (Chapter VIII). Accordingly, the patients deployed attention intermittently when performing at their best and the tendency increased as their performance deteriorated. This was supported by the between-subject analysis which
indicates (Figure IX.10) that errors invaded all subtest thirds at all levels of $M_I$ i.e., even before a ceiling of errors ($I_e 1.0$) was reached in any later third.

The between-subject analysis showed, too, that $I_e$ values increased as a function of subtest difficulty, in the order S1, F1, S2, and F2 at all levels of illness severity ($M_I$). This again vindicated the algorithm which showed (within-subjects) an increasing Pattern 3 frequency for the same subtest order.

The foregoing results indicate that schizophrenics pay attention intermittently and this limits their capacity to sustain attention. Also, the rate of intermittence increases, and sustained attention decreases, with both task difficulty and task duration over a very short period. Possible reasons for this impairment are discussed in Chapter X.
CHAPTER X

Attention, Working Memory and Integration: A Neurological Model of Cognition and Schizophrenia

1 INTRODUCTION

In this concluding chapter an interpretation will be given for the sustained attention defect of schizophrenics demonstrated in Chapter IX. The defect, however, is not able to explain all symptoms of schizophrenia. In order to advance the discussion it will be necessary to outline a model of normal cognition, giving it a neurological basis which would account for the phenomenon of attention. The model is then applied to schizophrenia to explain the present findings and to suggest possible locations for the underlying pathology.

2 THE ATTENTION DEFICIT OF SCHIZOPHRENIA

Schizophrenic attention was intermittent and the rate of intermittence increases as task difficulty and duration increase (Chapter IX). What might produce this pattern of attention? One possibility is that intermittent disattention was caused by lapses of arousal or 'microsleeps' (e.g., Tiplady, 1992). However, low arousal would not account for the present results since the patients performed better when treated with the sedating neuroleptic CPZ (Chapter IV). Another possibility is that patients were distracted from the task. However, external distractors were attenuated by the experimental setting, and the decoy distractors ('wrong-ear targets') were largely ignored. On the other hand, internal distractors (thoughts) may have been more potent. However, these would be supposed to occur sporadically during all subtests (on average equally), throughout the subtests, and not more frequently in later thirds.

Instead, the variation of intermittent attention with task difficulty and task duration suggests that the roles of effort and motivation are crucial to understanding PAT performance. In Chapter VIII it was argued that the PAT subtests provide worsening 'cost/benefit' ratios, because a higher density of attention (observing responses), amounting to 'cost' (Jerison and Pickett, 1964), is required by both the dichotic and fast modes of presentation, whereas all subtests provide 50 targets as reward or 'benefit' (op. cit.).

A motivational interpretation of PAT performance is contrary to reports for the Continuous Performance Test (CPT) which derived the quantity 'β' (of signal detection theory) thought to measure motivation (Swets, Tanner and Birdsall, 1961). Both the PAT and CPT discriminated between healthy subjects and schizophrenics (Chapter VIII; Comblatt and Keilp, 1994, review), but only d' of signal detection
theory (measuring detection accuracy) did so for the CPT (β did not). However, the scoring method of the CPT invalidates the use of signal detection theory (Chapter VII), the theory is probably inapplicable to suprathreshold stimuli (Pigache, 1976; Posner, 1980), and its assumptions are unlikely to be met by schizophrenics (Pigache, 1976). Moreover, the two quantities of signal detection theory become meaningless when subjects pay no attention to the task. Hence the assertion that motivational factors do not contribute to CPT errors because β was unchanged (Cohen and Servan-Shreiber, 1992) is unfounded.

Motivation results from the difference in value that subjects assign to alternative options (c.f., Premack, 1971). A ubiquitous option emphasized by Fowler (1971) and Premack (1971) resides in the existing situation or state of the subject, which provides a reference value when determining momentary preferences. Thus options include to do nothing or scan the environment (Fowler, 1971). Since incentive value refers to an expected outcome (‘reward’ or ‘punishment’) it relies upon inference (based upon knowledge). Value has been viewed as an affective judgement which lies along a dimension of preference (Fowler, 1971; Premack, 1971; Zajonc, 1980). Affect (value) is encoded directly and automatically without any need for cognitive analysis (Zajonc, 1980).

The matter of what is rewarding (the type of stimulus or event) appears to be ‘almost anything’ depending mostly upon the antecedent condition (Fowler, 1971; Premack, 1971). The concept of reward was reviewed recently and extended to include cognitive acts and thoughts (Miller, 1993, pp. 164-169). The incentive property of serial successive discrimination tasks such as the PAT lies in their intrinsic interest and in the reinforcement provided by correct detections (Jerison, 1970). Moreover, the momentary value of performance appears to increase when reinforcement seems imminent and to decrease with satiation. Prolonged exposure to task stimuli results in ‘stimulus satiation’ (Fowler, 1971) or ‘adaptation’ (Jerison, 1970). Thus as the value of performance diminishes competing options become relatively more attractive and may momentarily divert attention. This would be more pronounced with increases of task difficulty and duration, as observed with many tasks including the PAT.

Performance of the PAT requires a behavioural ‘set’ or plan. Plans possess goals (intentions) which also have value\(^{11}\), and they control operations (Miller, Galanter and Pribram, 1960). Plans operate ‘top-down’ and deploy all manner of resources (rehearsal, search, motor, etc.) which would include attention, as follows.

\(^{11}\) It is interesting to note here that Miller (1993) views reward as attached to intentions rather than to responses (which vary in their topography).
Attention has been compared to a spotlight (Norman, 1968; Posner, Snyder & Davidson, 1980) acting to facilitate the processing of specific inputs (Bushnell, Goldberg & Robinson, 1981; Spitzer, Desimone & Moran, 1988; Corbetta et al., 1990; Posner and Dehaene, 1994); and as a resource to be deployed (Kahneman, 1973; Wickens, 1980). The various modes of attention may be considered as parameters set up by plans to direct attention towards particular inputs. Thus plans would orient receptors towards a source of input, and would specify the perceptual locus ('stimulus-set'), any subsequent loci (switching of attention), the bandwidth of the spotlight (span of attention), when attention is needed, and the duration of an attentional act (brief, and unrelated to sustained attention).

Plans must resist competing options which would capture the resources they deploy. Distraction occurs when the incumbent plan, or that part of the plan controlling attention, is displaced by a competing option with a higher momentary value. Thus an exacerbation of the competition for any reason would lead to impaired PAT performance, as in schizophrenia. The outcome of such disruption resembles the "segmental set theory" of Shakow (1977) which suggests that the primary defect of schizophrenia is a transfer of control from major adaptive sets to minor 'segmental sets' which are inappropriate and poorly constructed. Although the theory accounts for certain symptoms of the illness the loss of 'set' may be more a consequence than the cause of schizophrenia.

Whereas plans direct attention in a top-down manner competing options may represent 'bottom-up' processing. Options probably originate from widespread sources of parallel external and internal input, as products of automatic processing. Value is accorded to them by the associative knowledge net, which also gives value to novel input. Options deploy resources when adopted as plans. One example of a successful option is the startle response which momentarily replaces an incumbent plan. It might be reasonable to assume that a preferred option is usually selected (Estes, 1969). However, such a policy would make all choice hedonistic. Hence it is realistic also to assume that preferred options are often inhibited. In these circumstances it is likely that the incumbent plan must inhibit its rivals in order to prevail and that the inhibition is felt as effort. This capacity to inhibit would be necessary for a plan to sustain the focus of attention. The subjective magnitude of such effort may be inversely related to the incentive differential (difference between the momentary values of options and the plan):

"Nothing is really work unless you would rather be doing something else"

(J.M. Barrie).
James (1890) distinguished between active or voluntary attention, and passive or involuntary attention. Subjective qualities (volition, effort, etc.) are often attributed to attention, possibly because attention is so powerfully associated with awareness and our experience of the world. As a result we are less conscious of the plans controlling attention. Here, a different perspective will be proposed which distinguishes between plans applying active or passive control, with attention at the disposal of either. Plans which exert active (top-down) control (impositional plans) do so variously, e.g., by acting upon the environment so that it yields the desired result and information; by working on information using 'controlled processes' such as 'rehearse', 'translate', or 'calculate' (Shiffrin and Schneider, 1977); or by scanning information and matching it against a detection criterion; the execution of such plans may be effortful. Plans which permit passive control (non-impositional plans) specify the general context and hold off distractors, but allow 'automatic processes' (Shiffrin and Schneider, 1977) to operate (bottom-up) and shape the input, e.g., the plans commonly adopted during listening or watching ('automatic detection': Kahneman, 1973) which require no effort. More complex plans (superordinate) often combine sequences of active and passive control (c.f., Shiffrin and Schneider, 1977). Impositional and non-impositional plans also differ in other respects to be described later.

Involuntary attention' (distraction) corresponds to the non-voluntary displacement of an incumbent plan by an option which redirects attention. An example is the orienting response, which by its organization (e.g., Lynn, 1966) illustrates the subordination of attention to a plan, in this case an automatic plan: arrest of movement, head and body turning, orbital, pupillary, pinna and tympanic muscle responses, autonomic responses (heart rate, sweat glands, respiration, vascular), and central arousal. "Automatic attention responses" (Shiffrin and Schneider, 1977) occur to salient input and result from bottom-up processes which require no effort.

If the intermittent attention of schizophrenics when performing the PAT is the result of preferred options momentarily replacing the plan, as above, the present discussion turns full circle to face once more the topic of selective attention. Moray (1969) described selective attention as the ability to focus upon one source of input while excluding simultaneous distraction. However, attention is by definition selective: it fastens upon a subset of the input. Accordingly, the selection of a plan is the critical step which determines the terrain upon which attention will play. As a consequence, selective attention and sustained attention represent one parameter of a plan, and are no longer parameters of attention; they operate together. If a selected

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12 If the usurping plan continues to control the focus of attention it rapidly acquires the active status and may feel voluntary again.
plan directs attention towards a particular stimulus source it is sustained for a finite
period; alternatively, the maintainance of a plan sustains all parameters of attention
it directs towards the specified source.

Cohen and Servan-Schreiber (1989) regarded selective attention as "the
mediating effects that context has on processing" and ascribed the CPT impairment
of schizophrenics to a degradation of memory for the context. This interpretation was
restricted to conditional versions of the CPT where a stimulus qualifies as a 'target'
only if it follows a specified predecessor. In present terms: when a plan involves a
sequence of steps each dependent upon the outcome ('meaning') of its predecessor and
an outcome is uncertain (or its trace decays) performance will suffer; hence the
motivational value of the plan will diminish relative to rival options. The foregoing
explanation, however, does not apply to the PAT since the task imposes no memory
load. Moreover, the observed intermittence of attention indicated that the patients had
not forgotten the prior instructions when attention returned to the task.

Hence the PAT findings may be interpreted as follows. Spontaneous internal
distractors, occurring on average equally throughout all subtests, would have disrupted
performance when their salience (relative value) increased during the difficult subtests
and later thirds, as task motivation waned. The patients own thoughts were probably
more important to them than the PAT targets and provoked automatic attention
responses. In this situation the plan controlling PAT performance would not have
mustered sufficient inhibition to maintain its dominance; the task had become too
effortful. Conversely, the inability experienced by schizophrenics with mainly
negative symptoms to adopt an alternative option (abulia or avolidon) might indicate
a failure to inhibit the incumbent plan.

An extensive body of evidence demonstrates that schizophrenics are abnormally
prone to distraction (Grillon et al., 1990; Miller, 1993: review). Is it possible that
schizophrenics activate more associated material from memory than is normal, which
then reaches awareness by overwhelming a normal capacity for inhibition; or, do they
activate quite normally a large quantity of material which reaches awareness solely
because they lack the normal capacity to inhibit irrelevant and incongruous items?
The former possibility may be insufficient to cause schizophrenia because heightened
distractability, elicited by external or internal stimuli, is common to many conditions
other than schizophrenia, e.g., mania, generalized anxiety disorder, the attention deficit
disorder of children, amphetamine intoxication, and delirium (American Psychiatric
Association, 1980). Accordingly, the second possibility should be considered in
greater detail. One theory of schizophrenia proposed by Frith (1979) and Joseph, Frith
and Waddington (1979), recently elaborated upon by Miller (1993), points to a failure
of mutual inhibition. Both versions of the theory identify the striatum as the site of this inhibition. Reciprocal inhibition (c.f., Shallice 1972; Walley and Weiden, 1973) between striatal γ-aminobutyric acid (GABA) neurones would result in the most strongly activated neurons inhibiting all less activated neighbours, and would serve as the basis for plan selection (Penney and Young, 1983) as described earlier. Thus a failure of reciprocal inhibition would leave competing options unadjudicated.

Joseph et al. (1979) attributed the proposed failure to excessive dopamine activity caused by overarousal in a genetically predisposed subject. Miller (1993) argued that an overactive dopamine system would invest all options with the same high incentive value, thus eliminating the differential quantity that enables a resolution by mutual inhibition. Both explanations, however, are weakened by the admitted lack of direct evidence for 'dopamine overactivity' in schizophrenia (Miller, 1993, p. 213). Also, though the dopamine hypothesis may find support in the earlier observation that chlorpromazine improved the PAT performance of schizophrenics (Chapters IV and V), it is challenged by many other findings. Thus neuroleptics do not cure schizophrenia: up to 30% of patients are non-responders and another 30-40% of partial responders persist with psychotic symptoms (Davis and Casper, 1977; Lewander, 1992); the therapeutic benefits of neuroleptics are not specific to schizophrenia (Healy, 1991); long latencies of recovery and relapse are observed when neuroleptics are given or stopped (e.g., Chapter IV); schizophrenia is not exacerbated by L-dopa or d-amphetamine (Alpert and Friedhoff, 1980; Christison, Kirch, and Wyatt, 1991); and amphetamine psychosis does not reproduce the core symptoms of schizophrenia (Joyce, 1988). Accordingly, the dopamine hypothesis of schizophrenia is now being abandoned, e.g., Carlsson (1990). Whereas there is little doubt that the therapeutic effects of neuroleptics derive from their blockade of dopamine receptors (review: Healy, 1991) a rather different theory is needed for schizophrenia itself. Such an hypothesis needs to explain schizophrenic distractibility and the many other symptoms of the illness. Nonetheless, it is not necessary to reject the previous proposal that a failure to engage inhibitory processes may contribute to schizophrenia.

A MODEL OF NORMAL COGNITION

Performance of complex tasks such as the PAT involves an interplay between controlled operations, which require attention, and automatic operations which do not (Shiffrin and Schneider, 1977); in such situations plans automatically 'tune' attention
to the task requirements. For example (steps related to attention in italics): the plan might first orient the subject's receptors towards the source of input and bias sensitivity in the relevant perceptual systems; it might then engage automatic operations (bottom-up) to begin processing the input; the plan would then await an automatic 'detection call' (from a brain location appropriate to the task and level of analysis) when processing is complete; after this the plan would direct attention to the result, make a decision, and finally instigate a response.

It is now suggested that the distracting options which subvert the plans of schizophrenics result from an apparent defect of integration, a process described by Kintsch (1988) in a model of discourse comprehension. The cause of the defect, however, might be indirect. Integration is part of a highly flexible, automatic and bottom-up process "construction-integration" which operates fast and effortlessly to create new 'meaning' on-line as contexts change. Unlike top-down models of discourse comprehension (the majority) the Kintsch model does not rely upon experience and prior expectations to filter out inappropriate meanings, or to predict the sense of incomplete sentences. The production rules of top-down models lack the flexibility necessary to anticipate correctly the vast range of future situations and their contexts. However a recent top-down model (not based upon attention) was applied to schizophrenia and did account for distractors (e.g., hallucinations, thought insertion), by postulating "parasitic foci" in networks of neurones (Hoffman and McGlashan, 1993).

Although the model described by Kintsch is not limited to discourse comprehension it will be summarized in that context. As a text is read automatic encoding creates a set of word candidates which activates near neighbour associates in a network of propositional knowledge and the construction phase begins; some of the net is raised from long-term storage (LTS) to short-term storage (STS). One result is that antonyms and different meanings of ambiguous words may be activated at random (c.f., Onifer and Swinney, 1981), likewise for propositions (concepts) and inferences. The final step of construction is to inventorize the strengths of all interconnections between the various elements of the haphazard structure in STS (a connectivity matrix is created). Then the integration phase begins which incorporates context and repeatedly activates the matrix. Construction-integration repeats in cycles and operates upon increasingly more elaborate constructions, until new cycles fail to

13 Automatic attention operations are deployed by plans and were termed "tuning" by Moray (1969). These operations comprise highly overlearned attentional skills which begin to be learned in infancy. They would include "automatic detection" (Kahneman, 1973) and similar responses described by Shiffrin and Schneider (1977) and require no effort; any inhibitory effort needed would be supplied by the controlling plan. Such automatization increases capacity and the scope of planning (Miller, Galanter and Pribram, 1960).
change the structure significantly and the system stabilizes. The process of integration strengthens the strong connections between propositions, the context and the knowledge net, and weakens other connections. Eventually, meanings inappropriate to the discourse context are eliminated and a plausible meaning is both identified and located within the knowledge net. The level of comprehension reached by construction-integration depends upon the time available and the incumbent plan (c.f., Craik and Lockhart, 1972). Kintsch (1988) also showed that his model applies to verbally presented arithmetical problems, and envisaged that it might extend to the processing of non-verbal and affective information. The model is supported by experimental data using priming methods and by a computer simulation.

Context is critical to the editing role of integration and is incorporated only at integration. It should be noted that during the construction phase associates at any level of representation become activated without reference to the context. Afterwards, the integration process draws upon whatever material is currently held in the STS buffer (context in working-memory) together with its affective connotations and applies it to the connectivity matrix. The result of each integration is carried over likewise to the next integration phase. The Kintsch (1988) model stops at this point. In the terminology of this chapter experiential context supports integration performed by non-impositional plans, which allow bottom-up automatic operations to control the flow of information. However, impositional plans which exert a top-down control over information processing would bias integration by applying additional constraints, e.g., by introducing into the purposive context a template for input-matching during a detection task (c.f., Rumelhart and McClelland, 1982). Attention is paid at the moment of decision. The purposive context of a plan operates to exclude rival response options.

The cognitive model outlined, above, embraces two possible malfunctions either of which would be manifest as impaired integration. The first is a failure of integration itself and the second a loss of context (degradation or decay). Both would cause similar editing failures resulting in distraction or a switch of plan. If schizophrenia entails defective integration the relevant defect ought to be identified. The task might be made easier by casting the cognitive model in neurological terms.

3.1 NEUROLOGICAL MODEL

An embodiment of the foregoing model in terms of neurological structure and function will now be attempted. The aim may be ambitious, but if the argument is kept sufficiently general the effort might succeed and prompt interesting speculations, perhaps leading to useful hypotheses. Accordingly the various cognitive operations
described, above, will be considered in relation to plausible brain locations (Figure X.1).

First, it seems reasonable to assume that construction would be the primary function of cortex because of its excitatory, divergent, and reciprocal corticocortical connections (involving both hemispheres and the hippocampal complex). Even at a local level cortex maximizes the diversity of its inputs. Many afferent axons terminate in patches, out of register with the underlying cortical columns, so that each superficial neurone samples a unique mix of patch and inter-patch inputs (Malach, 1994).

Second, the experiential context (result, or 'meaning' of the last integration cycle) is probably maintained by reciprocal corticothalamic circuits involving the mediodorsal thalamic nucleus (i.e., experiential working-memory). The cortical projection field of the mediodorsal nucleus was taken to define prefrontal cortex (Rose and Woolsey, 1948) including, too, anterior cingulate cortex. Layer VI of cortex projects to the thalamus (Jones, 1976) which projects back to cortical layers IIIb and IV (Jones, 1975; Jones and Burton, 1976). This re-entrant pathway provides positive feedback to stellate cells in layer IV which are strongly connected to cells in layers II, III and V (Jones, 1975), and make cartridge synapses (Szentagothai, 1969) along the lengths of apical dendrites from deep pyramidal cells. Repetitive firing of this reverberatory circuit is thought to subserve a memory function (Eccles, 1981). Atrophy of the mediodorsal nucleus causes 'diencephalic amnesia' (e.g., Korsakoff's syndrome), attributed to an impaired acquisition of contextual information (Stern, 1981; Hirst, 1982; Squire and Cohen, 1984). A lesion limited to this nucleus (verified by CT scan) in Case NA produced deficits similar to Korsakoff's syndrome (review: Squire and Cohen, 1984). Equivalent lesions to rats (e.g., Kessler and Markowitsch, 1981) and monkeys (Aggleton and Mishkin, 1983) similarly impair delayed alternation or delayed non-matching-to-sample performance. Excitatory activity within the mediodorsal thalamic nucleus was observed during the delay period of a delayed response task (Fuster and Alexander, 1973). In addition, mnemonic 'delay cells' are activated in the dorsolateral prefrontal cortex during the delay period of delayed response tasks (Fuster, 1984; Goldman-Rakic, 1985). The functional integrity of dorsolateral prefrontal cortex is also essential to tasks involving working memory (e.g., Milner and Petrides, 1984). As followed the thalamic lesions, above, rats (Granon et al., 1994) and monkeys (e.g., Pribram, 1961) with prefrontal lesions were impaired when performing delayed alternation or delayed non-matching-to-sample tasks. Hence
FIGURE X.1  Neural circuitry for construction-integration. The example depicts two columns (layers I to VI) from two cortical regions: dorsolateral prefrontal cortex (dPFC) and posterior parietal cortex (pPC) which are reciprocally connected (dotted lines). The projection from dPFC deploys attention (large dots); both pathways are active during construction. Excitatory reciprocal corticothalamic circuit (thick lines) via the mediiodorsal thalamic (MD) and ventral anterior thalamic nuclei (VA) represent working-memory (★) for ‘meaning’ and the plan, respectively. The long loop from dPFC to caudate nucleus (CN), to the globus pallidus and substantia nigra pars reticulata (SNr), returns to control thalamic activity. Tonic inhibition of the thalamus by GP/SNr is modulated by the inhibitory output of the caudate nucleus. ‘Globus pallidus’ includes the pars interna (GPI) which projects to the thalamus and the pars externa (GPe) which with the subthalamic nucleus forms an important subsidiary circuit and further modulates GPI/SNr. Integration occurs within CN, selected input and plans are compiled in GPI/SNr. A reciprocal thalamic circuit between pPC and the pulvinar is omitted for the sake of clarity (the pulvinar is not modulated by GPI/SNr).
it is probable that prefrontal cortex and the mediodorsal thalamic nucleus together maintain working-memory.\textsuperscript{14}

Third, integration is almost certainly performed within the striatum (caudate nucleus, putamen and nucleus accumbens), e.g., Alexander and Crutcher (1990). It therefore stands in contrast to construction, since the striatum applies inhibition to excitatory input converging from all regions of cortex. Only five areas of pre-Rolandic cortex receive return projections from the basal ganglia (striatum, and pallidum) as shown in Figure X.1, namely dorsolateral prefrontal, lateral orbitofrontal, anterior cingulate, frontal eye-field, and precentral motor cortices (reviews: Alexander, DeLong and Strick, 1986; Alexander and Crutcher, 1990). These privileged areas of cortex (and their subareas) project to segregated striatal domains, and are connected reciprocally to association cortex which projects in an interdigitated manner to the same striatal domains, thus function is conserved within the domains (Alexander, DeLong and Strick, 1986). Accordingly, integration is restricted to separate parallel domains and to narrowly pertinent information. However, the model requires two sources of input for integration i.e., context and the connectivity matrix at the end of each construction phase (Kintsch, 1988). Hence it is proposed that context is transmitted to the striatum by the excitatory corticostriatal efferents from the privileged cortical areas, above; and that the connectivity matrix is encoded by the extensive corticostriatal projections from sensory association areas, which receive no return from the basal ganglia (Alexander, DeLong and Strick, 1986). This schema agrees with Marsden and Obeso (review: 1994) who remark that "The overall picture of striatal activity thus is dominated by its inputs, and by the contextual significance of environmental and perhaps internal cues". Indeed, the striatum has often been regarded as a 'gate' selecting motor, cognitive, or other types of behaviour and suppressing competing options (Stevens, 1973; Divac, 1977; Cools, 1980; Penney and Young, 1983; Marsden, 1987; Miller, 1993).

In order to integrate context with the connectivity matrix the two sets of input must converge. It was shown, however, that axon terminals from the pyramidal cells of layer Va (Jones et al., 1977) in distinct cortical areas do not intermix, but form a complex mosaic within the striatal matrix compartment (Selemon and Goldman-Rakic, 1985). The size of these axonal patches suggested to many authors a correspondence to cortical columns (Kunzle, 1975; Jones et al., 1977; Goldman and Nauta, 1977; Yeterian and Van Hoesen, 1978; Selemon and Goldman-Rakic, 1985). Moreover, cells of the striatal matrix form clusters with similar dimensions to the axonal patches

\textsuperscript{14} A similar reverberatory function between cortex and thalamus in more posterior regions might underlie also a wide distribution of working-memory (Frackowiak, 1994), or possibly sensory-memory.
This arrangement (found also in the thalamus) suggests a further principle of neural organization, so far described only for cortical columns (Malach, 1994). Thus axons from a given source terminate in patches out of register with cell clusters (or columns) but of similar dimensions, so that each cell in the cluster samples a unique mix of patch and inter-patch inputs (op. cit.). The register between axon patches and cell clusters in the striatum is not known, but a pattern of cell clusters within separate striatal domains makes sense. It would ensure that information delivered to a cell, currently inhibited by integration within one domain, is not needed simultaneously for integration occurring elsewhere. Integration itself would be achieved by mutual inhibition (e.g., Joseph, Frith, and Waddington, 1979; Penney and Young, 1983; Groves, 1983) between the richly interconnected output neurons of each striatal domain. Thus in terms of the present model haphazard associations, activated throughout the cortical network, are edited in relation to context by mutual inhibition within segregated striatal domains.

Fourth, cell clusters of the striatal matrix send their inhibitory output to the basal ganglia (globus pallidus, substantia nigra pars reticulata, and ventral pallidum). Note that Figure X.1 provides an oversimplified version of basal ganglia connectivity. Detailed accounts of the anatomy, neurotransmitter relationships, and function of the basal ganglia can be found in recent reviews (Alexander and Crutcher, 1990; Parent, 1990; Graybiel, 1990; Di Chiara, Morelli and Consolo, 1994; Marsden and Obedo, 1994). It is generally agreed, however, that individual neurones receive convergent input from a large number of striatal neurones which maintain their topographical organization and functional specificity (Alexander, DeLong and Strick, 1986; Alexander and Crutcher, 1990). The purpose of this convergence may be to compile the total output relating to an integrated ‘meaning’ or plan within the scope of each segregated pathway (Chevalier and Deniau, 1990). The pallidal/nigral neurones maintain the segregation in their projections back to thalamic nuclei which are dedicated to the five privileged cortical areas, described earlier (Alexander, DeLong and Strick, 1986). Under rest conditions the pallidal/nigral neurones tonically inhibit their thalamic neurone targets (Penney and Young, 1983; Alexander and Crutcher, 1990). Accordingly, the striatal inhibition of pallidal/nigral output facilitates positive feedback in the corresponding corticothalamic loops, resulting in a net modulation of thalamic activity.

15 The clusters are distinct from the matrix and striosome organization within the striatum (Graybiel, 1990).

16 A plan can be regarded as an alternative expression of ‘meaning’ since its application indicates a particular interpretation of the world.
A notable feature of the pallidal/nigral projection to the thalamus is that two thalamic nuclei are targeted per principal cortical area, except for the anterior cingulate cortex. Each prefrontal area is reciprocally connected to subsections of both the mediodorsal and ventral anterior thalamic nuclei (Figure X.1). Evidence was presented earlier indicating that the mediodorsal nucleus maintains the most recent result of integration in experiential working-memory. Information transmitted by the pallidal/nigral projection to the mediodorsal thalamic nucleus would therefore update working memory and the context with the 'new meaning' extracted by integration. Modulation of this nucleus would cause it to facilitate a pattern of correspondingly activated cortical columns, which in turn would participate in more intricate patterns of activation reflecting the 'new meaning'. The pattern of activity maintained by the mediodorsal thalamic nucleus might resemble or correspond to the experiential context required for the next integration phase.

By contrast, the ventral anterior thalamic nucleus may be more related to plans and top-down operations since it belongs to the ventral tier of thalamic nuclei, and its parvocellular division possess separate zones for premotor and prefrontal cortex. Hence its positive feedback loop with prefrontal cortex might maintain the current plan in purposive working-memory. This maintained activity would also provide the striatum with purposive context as required for the next integration phase. Modulation of the VA circuit by the pallidal/nigral projections would either update the current plan (prompting sequences of operations) or replace it. Response options which may replace the plan, and the next step of an evolving plan, are represented by activity in other prefrontal networks (but may be elaborated more widely in the brain). Options, however, are not yet plans hence they are not supported by reverberatory thalamic feedback and do not provide the purposive context. In order to be adopted they must

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17 The basal ganglia-thalamocortical circuit subordinate to anterior cingulate cortex projects only to the mediodorsal thalamic nucleus (Alexander, DeLong and Strick, 1986). However, the anterior cingulate cortex is connected reciprocally to the anterior thalamic nucleus (dorsal to the ventral anterior nucleus) which forms part of Papez's circuit. The latter nucleus is modulated by the mamillary bodies which might substitute for the 'missing' striatal input. The modulation possibly implements learned behaviour patterns (automatic plans) indexed by the hippocampus.

18 A recent review by Groenewegen and Berendsse (1994) demonstrates that the thalamic midline-intralaminar nuclear complex projects, too, in an organized manner to the cortical and striatal locations specific to recursive basal-ganglia-thalamocortical circuits. These nuclei represent a rostral continuation of the non-specific ascending reticular activating system and transmit affective and alerting aspects of information. Electrical stimulation of the brainstem reticular formation arrests plans via the same pathways (Yingling and Skinner, 1977).

19 Response options may be generated as associates of the input and are thereby activated during the bottom-up construction of 'meaning' at any level. Options created by top-down planning are different. The latter are produced by an incumbent plan and so represent controlled construction that uses attention.
first recruit a strongly associated network of elements (the strength of certain associations may denote 'value'). The connectivity matrix is then transmitted to the striatum by corticostriatal projections, parallel to those of the incumbent plan, and there must inhibit the plan for the option to be adopted. At integration the strength of a plan would increase with the redundancy of its purposive context. Redundant context might entrain a network of striatal inhibition sufficient to suppress rival options; otherwise the plan might undergo modification or be replaced by a potent option. The resultant plan then reaches prefrontal cortex via the ventral anterior nucleus which maintains it in operative working-memory.

It follows from the model that working-memory is symmetrically organized as two complementary circuits in prefrontal cortex. One circuit (via the mediodorsal thalamic nucleus) mediates the present 'meaning' and sustains the experiential context necessary for integration; the other circuit (via the ventral anterior nucleus) mediates the corresponding plan and sustains the purposive context for integration. Accordingly, the reverberatory corticothalamic circuits maintain both a 'meaning' and a plan, which in turn deploy attention. A basis for attention will now be proposed.

The neural mechanisms of attention may be found on-site within the columns of anterior cingulate and prefrontal cortex. The anterior cingulate cortex has been identified by positron emission tomography (PET) studies as part of an "anterior attentional system" (Posner et al., 1988; Pardo et al., 1990; Pardo, Fox and Raichle, 1991; Posner and Dehaene, 1994). Likewise, it was recently shown that glucose metabolism in a middle region of prefrontal cortex increased when healthy subjects performed the Continuous Performance Task, which requires sustained attention (Cohen et al., 1987). How might attention be mediated?

Return projections to cortex from both the thalamus terminate in layers III and IV of cortex (Jones, 1975; Jones and Burton, 1976). Corticocortical projections from prefrontal cortex emanate from pyramidal cells of layers III, Vb and VI (Barbas, 1986). Hence cells that mediate attention are to be found in these layers. Axons of cells in the deep layers travel more distantly and these cells more often project to highly differentiated cortex such as the sensory cortices. Axon terminals are distributed throughout the columns of the recipient cortex, but in highly differentiated cortices are found most abundantly in layer I (Barbas and Pandya, 1989). Hence current information held in experiential working memory, and the plan in operational working memory, are both relayed to their respective output cells in layers III and VI, and cells in the same layers are well connected to enhance activity in other cortical...

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20 The tactical deployment of visual attention also activates circuits in the parietal cortex, pulvinar, and superior colliculus (Posner and Petersen, 1990; Posner and Dehaene, 1994).
areas i.e., to direct the spotlight of attention and facilitate input. In terms of the present model options constructed in cortex, selected by the basal ganglia, and maintained by recurrent thalamic circuitry, become plans with the means to deploy attention.\textsuperscript{21} The present view of attention differs substantially from the attention models of Mesulam (1981), Cowan (1988), and Näätänen (1990), but includes common elements.

4 THE MODEL APPLIED TO SCHIZOPHRENIA

Two features of the Kintsch model and its present extension are highly pertinent to schizophrenia. First, the presence in STS of remote, sometimes bizarre, material as in schizophrenia (e.g., Moon et al., 1968; Sengel and Lovallo, 1980; Solovay, Shenton and Holzman, 1987) is made a natural event. Although we are not normally aware of this material its activation is no longer unique to psychoses, and its source needs no further postulate (contra: Hoffman and McGlashan, 1993). A spontaneous activation of sensory circuits (e.g., Farah, 1989) would similarly account for hallucinatory sensory images during normal relaxed wakefulness (Foulkes and Fleisher, 1975), hypnogogic states (Mavromatis, 1987), the content of dreams during rapid eye movement (REM) sleep (Foulkes, 1982), and hallucinations (review: Asaad and Shapiro, 1986).

Second, the process of integration performs a critical editing function which uses context to eliminate irrelevant and nonsensical material. A normal suspension of integration during REM sleep would explain the absence of "reality tests" during dreams (Hartmann, 1975). A pervasive failure of editing has been suggested for schizophrenia (Hemsley and Zawada, 1976; Cohen, 1978), which Harrow et al. (1983) termed 'impaired perspective'. If integration is impaired the construction phase might run-on and activate even more invalid propositions and inferences calling for attention (c.f., Freedman, 1974). When construction-integration does not stabilize the search for 'meaning' requires "focused problem-solving operations" (Kintsch, 1988) performed slowly by plans reliant upon attention. Attempts by schizophrenics to search for 'meaning' might also be vitiated by the decay of material from working-memory, degraded context, and a corrupted knowledge net.

Irrelevant material associated with a percept or thought is often activated in schizophrenia (e.g., Lawson, McGhie and Chapman, 1964; Andreasen, 1979; Miller, 1993, review). Likewise, the patients exhibit broader stimulus generalization (Ralph, \footnote{Thus syndromes of unilateral neglect do not indicate defects of attention (contra: Mesulam, 1981), but denote an absence of output from the lesioned brain areas during the construction of options and plans, thereby deleting all operations (including the deployment of attention) relating to functions that have ceased to exist.}
1968) and "overinclusive" behaviour, indicating that the adopted option was a loose associate of a more appropriate alternative [see Miller (1993) whorevives the concept of "widened conceptual boundaries" in schizophrenia as first described by Cameron (1938)]. A failure to integrate experience with its context would also account for the alien (non-self) quality of many schizophrenic symptoms, e.g., hallucinations. Lastly, the salient quality of incongruous stimuli would capture the attention of schizophrenics and cause distraction (Kay, 1982). The neurological model of cognition just described will now be applied to schizophrenia in order to identify the locus or loci where dysfunction might occur.

4.1 Striatal dysfunction

Is integration actually impaired in schizophrenia? The present neurological model assigns integration to the γ-aba output cells of the striatum. However, gross pathological abnormalities of the striatum post mortem have not been observed in schizophrenia, which is normal both in volume (Bogerts, Meertz and Schönfeldt-Bausch, 1985) and cell number (Dom et al., 1981). Earlier studies are difficult to interpret because of diagnostic and laboratory procedures (Weingartner, Wagner and Wyatt, 1983), but histological abnormalities of the striatum have been reported in schizophrenic brains removed during the pre-neuroleptic era (Davison and Bagley, 1969; Stevens, 1982). Two studies described morphological features in the basal ganglia which appeared pathological, and another two reported 'dwarf cells' in patients with catatonic schizophrenia (cited: Stevens, 1982). More recently, Dom et al. (1981) observed that small Golgi type II neurones were significantly smaller in the nucleus accumbens of catatonic schizophrenics as compared to normal brains from the Vogt collection (pre-neuroleptic era), with a fifty-percent reduction of larger cells (Dom et al., 1981). The latter observation was confirmed by Pakkenberg (1991). Also, the distribution of monoamine receptors between matrix and striosomal compartments of the striatum may also be abnormal in unmedicated schizophrenics (Joyce, 1992). In summary, though none of the foregoing observations suggests a structural abnormality in the dorsal striatum affecting the major population of output cells, severe pathology occurs in the ventral striatum and is likely to disrupt integration.

One hypothesis of schizophrenia (van Kammen, 1977) suggested that low striatal γ-aba activity causes diminished inhibition of dopaminergic neurones in the substantia nigra pars compacta and ventral tegmentum (via striatonigral pathways). Two of three studies reviewed by Meldrum (1982) reported significant decreases of γ-aba concentration in the striatum (nucleus accumbens) of schizophrenics as compared to healthy subjects. Also, high doses of pre-synaptic γ-aba-agonists (administered
parenterally) e.g., muscimol and baclofen, may induce an acute toxic psychosis in healthy subjects and exacerbate psychotic symptoms in schizophrenics (Meldrum, 1982; Lloyd and Morselli, 1987), but the site of action is unclear. By contrast, benzodiazepines which bind to sites associated with post-synaptic γaba receptors, produce rapid therapeutic benefits for some schizophrenics when added to a neuroleptic regimen (Pecknold, 1993). They reduce many symptoms of schizophrenia including hallucinations and delusions, but mostly benefit patients with severe psychotic symptoms, and patients unresponsive to neuroleptics (reviews: Christison, Kirch and Wyatt, 1991; Wolkowitz and Pickar, 1991). Benzodiazepine withdrawal also precipitated psychotic symptoms in schizophrenics which exceeded the original severity (Wolkowitz et al., 1986 and 1988). A suggested mechanism for this benzodiazepine action, similar to that of Van Kammen for schizophrenia, was inhibition of dopamine neurotransmission and release (Wolkowitz and Pickar, 1991). However, an additional possibility, relevant to the present hypothesis, is that γaba transmission was also increased in the striatothalamic circuit (effects produced at other loci cannot be excluded).

The findings reviewed, above, are compatible with the suggestion that striatal pathology would contribute to the symptoms of schizophrenia, but the frequency of such pathology might be rather low and more often indicative of Huntington’s disease (Lange et al., 1976). However, the striatum lies at the centre of a web and its capacity to integrate and edit efficiently would also depend upon the reliable transmission of contextual information through its recurrent corticostriatal loops. Thus a disruption of the afferent corticostriatal limb would impair integration (a functional defect) and result in aberrant ‘meaning’; and a disruption of the efferent striatocortical limb would corrupt the updated information sent back to working-memory. There is evidence that either or both pathways might be defective in schizophrenia.

4.2 Pallidal dysfunction

The globus pallidus and substantia nigra pars reticulata lie on the recurrent cortical/basal ganglia circuit. Striatal output cells project to the globus pallidus interna where a significant 20% reduction of volume was noted in schizophrenic as compared to normal brains, taken from the Vogt collection (Bogerts, Meertz and Schönfeldt-Bausch, 1985). Two neuropathological studies (Josephy, 1930; Stevens, 1982) reported calcifications in the globus pallidus of young schizophrenics. Stevens (op. cit.) also observed a marked loss of large pallidal neurones in three patients and pallidal infarcts in two others; all were diagnosed originally as catatonic and later as chronic schizophrenics, comprising 18% of the sample. Lastly, glucose utilization was
increased in the pallidum of drug-free schizophrenics (Wolkins et al., 1985; Early et al., 1987; Resnick et al. 1988) as compared to control subjects. Thus a role for the globus pallidus in the pathology of schizophrenia is possible.

4.3 Dysfunctional prefrontal cortex

Prefrontal cortex is at the summit of the recurrent loop through the striatum and its capacity to plan relies upon the information in working-memory that it automatically receives. Enlargements of the cerebral ventricles, frontal sulci, and the rostral interhemispheric fissure (reviews: Seidman, 1983; Roberts, 1990) are found in schizophrenics as compared to healthy subjects, suggesting tissue loss (McCarley et al., 1989); and the frontal lobes are smaller in schizophrenia (Andreasen et al., 1986). Two regions of this cortex were studied morphologically (lateral orbitofrontal cortex: Brodmann area 10; and orbital cortex: Brodmann area 11) in comparisons of schizophrenic and control brains, as follows. Area 10 showed a seventy-percent reduction of cells in layers IV and V (Colon, 1972). More recently, it was found to contain significantly fewer neurones in layers II, III and VI (Benes, Davidson and Bird, 1986); layer V contained neurones with more than one apical dendrite (Senitz, 1992); and layer VI showed an irregular arrangement of triangular cells with abnormal dendrites (Senitz and Winkelmann, 1981). Area 11 contained pyramidal cells with multiple apical dendrites in layer III, and cells in layer VI with abnormally ramifying apical dendrites (Senitz, 1992) and triangular cells as for area 10, above (Senitz and Winkelmann, 1981). Atrophy in layers II and III of frontal cortex was first observed by Alzheimer (1913) in schizophrenic brains; Benes (1993) found fewer interneurones in layer II; and atrophy of cortical layers III-VI was reported by Tatetsu (1964) and Wildi, Linder, and Costoules (1967). Cortical layers III-VI are important because they participate in several critical circuits of Figure X.1.

The pathological findings in areas 10 and 11 are possibly generalizable to other areas of prefrontal cortex since abnormalities in cortical layer III (sometimes deeper layers too) are reported for motor cortex (Colon, 1972; Benes, Davidson and Bird, 1986), cingulate cortex (Colon, 1972; Benes and Bird, 1987), ventral insular, and claustrum cortex (Jakob and Beckmann, 1989) in schizophrenia. Cortical columns in the anterior cingulate gyrus possess fewer interneurones and are more widely separated in schizophrenic as compared to control brains, suggesting an increased number of axons coursing between the columns (Benes, 1993).

The mediodorsal thalamic nucleus is integral to the circuitry of the prefrontal cortical layers III-VI. A smaller thalamus in male schizophrenics was found recently by magnetic resonance imaging (MRI) in a comparison with control subjects.
Abnormalities noted for the mediodorsal nucleus in schizophrenia include 'dwarf cells' (Vogt and Vogt, 1952) and frequent cases of fibrous gliosis (Stevens, 1982). The nucleus also suffered a pronounced loss of neurones amounting to approximately fifty-percent (Pakkenberg, 1990). These morphological abnormalities might disrupt the function of prefrontal and cingulate cortices in schizophrenia. A recent PET study showed that low glucose metabolism in the thalamus of drug-free schizophrenics correlated highly with the severity of illness, especially BPRS negative symptoms (Pickar, Hsiao and Litman, 1992).

In terms of the earlier model, the neuropathology just described might cause successive impairments of function as follows: structural pathology of the mediodorsal thalamic nucleus and prefrontal cortex would degrade experiential working-memory; abnormally functioning prefrontal cortex would construct poor quality options (including the next step of a plan), and would base these upon the degraded traces; hence options adopted as plans would lack quality; thus the purposive context applied to integration would be deficient; and this sequence would perpetuate itself. There is evidence for such defects in schizophrenia. For example, impaired working-memory was the explanation given for schizophrenic deficits of speech comprehension (Grove and Andreasen, 1985), speech production (Cohen, 1978; Rochester, 1978), short term recognition memory (review: Nuechterlein and Dawson, 1984), and faulty error correction during motor tasks (Kopp and Rist, 1994); and a similar deficit might account for the patients' inability to maintain a readiness to respond in reaction-time studies of the preparatory interval effect (reviews: Nuechterlein, 1977; Rist and Cohen, 1991).

In addition, schizophrenic speech demonstrates defective discourse-planning (Hoffman, Stopek and Andreasen, 1986; Solovay, Shenton, and Holzman, 1987; Thomas et al., 1990). It is therefore pertinent that semantic processing for subsequent speech activates prefrontal cortex, as was shown by a recent PET study of healthy subjects (Petersen et al., 1988). Schizophrenic speech is more difficult to reconstruct than normal speech (Rutter, 1977; 1985), utterances are typically short (Andreasen, 1979), less complex (Allen, 1983; Thomas et al, 1990), with poorly developed hierarchical substructures based more upon superficial associations than propositional relationships (Hoffman, Stopek and Andreasen, 1986), and demonstrates poor cohesion (Rochester and Martin, 1979; Hoffman Stopek and Andreasen, 1986). Another example of impaired planning by schizophrenics is their disordered performance of complex motor sequences, in tests involving repetitive hand positions which depend upon frontal lobe function (review: Heinrichs and Buchanan, 1988).
The Wisconsin Card Sorting Task (WCST) tests the functional integrity of the entire feedback loop between prefrontal cortex and the striatum, as depicted in Figure X.1. This task requires the subject to infer by trial-and-error the experimenter's undisclosed and changing principle for matching cards according to colour, form or number. First, it relies upon experiential working-memory (mediodorsal thalamic nucleus and prefrontal cortex) when the sorting basis changes without warning: the last sort-decision provides the experiential context which (after integration) gives 'meaning' to the experimenter's yes/no verdict, in the present case "No!". Second, a new response option must be created (prefrontal cortex) incorporating the new information as its template for matching. Third, after the option is adopted (striatum) as the new plan, it must be held in purposive working-memory (ventral anterior thalamic nucleus and prefrontal cortex). Thus the plan provides the purposive context (template) for integration with response options activated by the next card stimulus (which would include the previous, now 'wrong', response) in order to bias the classification. Schizophrenics are impaired on this task as compared to healthy subjects (Fey, 1951; Malmo, 1974; Weinberger, Berman and Zec, 1986; Morice, 1990; Weinberger, Berman and Daniel, 1992). For example, in a recent WCST study schizophrenics sorted by all manner of wrong hypotheses (Goldberg et al., 1987). When they were given card-by-card instruction performance improved, but afterwards the patients reverted to their original mode of performance "as if they were taking the test for the first time" and made perseverative errors; their performance, however, was not random. The authors remarked that "The hallmark of patients' behaviour was a failure to use feedback to alter response". By contrast the same patients were almost normal in list-learning and long-term recognition memory. The present interpretation is that degraded experiential working-memory and the poor quality of options, plans, and the purposive context (loss of redundancy) would lead to a defective control of striatal inhibition, permitting the emergence of stronger response options, including the repetition of a previously 'correct' response. However, as indicated above, impaired WCST performance is not restricted to schizophrenia. Patients with frontal lobe lesions (Milner, 1963; Milner and Petrides, 1984), Huntington's disease (striatal atrophy: defective integration) (Weinberger and Berman, 1985; Weinberger et al., 1988), or alcoholic brain damage (mediodorsal thalamic nucleus degeneration: defective working-memory) are all markedly impaired when performing this task (Tarter and Parsons, 1971; Malmo, 1974). These observations support the present

22 Parkinsonian patients are also impaired on the WCST (Taylor et al., 1986; Weinberger, Berman and Chase, 1989). The interpretation offered here for parkinsonism is that, normally dopamine permits behavioural switching by stopping the current plan (possibly by binding to inhibitory D2 receptors) and allowing the next plan to succeed. At the next integration context (now minus any 'set' of the old plan) applied to the new connectivity matrix selects the next plan. This plan now controls the context
model. Strauss and Klieser (1992) reported that WCST performance predicted subsequent clinical improvement, according to the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI) scores. Medicated schizophrenics tended to perform the WCST better than unmedicated patients, though the difference was not significant (Berman, Zec and Weingartner, 1986). Hence WCST performance may reflect neuropathology rather than a functional defect.

Vigilance tasks such as the CPT or PAT depend upon purposive working-memory and context (behavioural 'set') to maintain top-down control for the detection of target stimuli. A study of the CPT in healthy subjects showed that regional glucose metabolism in a middle region of prefrontal cortex (inferior to the dorsolateral area) increased significantly as compared to rest during a difficult version of the CPT, which also imposed a load upon experiential working-memory (Cohen et al., 1987). By contrast, the cortical metabolism of schizophrenics (whether medicated or not) was always significantly lower than normal (Cohen et al., 1988). Nonetheless, the CPT error rate and cortical metabolism were correlated both for healthy subjects and medicated schizophrenics. The lack of a similar correlation for drug-free patients was surprising and not explained (Cohen et al., 1987). It seems probable, however, that a dysfunction of this cortical area would have accompanied the impaired PAT performance (which did relate to the severity of illness) reported in previous chapters. The PAT, however, makes little or no demands upon experiential working-memory: the template for the target is consistent, well-practised, and not conditional; performance depends mainly upon 'set' maintenance and automatic detection. Accordingly, the PAT deficit of schizophrenics was attributed to intermittent attention. The present model attributes the PAT findings to the poor elaboration of plans in schizophrenia causing low redundancy ('noisy' purposive context) and diminished inhibitory synergism at the striatal level. As a result the total strength or 'value' of the plan would fall below that of salient momentary options competing for attention. Consistent with this interpretation schizophrenics in other tasks adopted low matching-criteria (Marchbanks and Williams, 1971), made more generalization errors (Mourer, 1973), and failed to edit districting material such that 'chunking' was disrupted (Oltmanns and Neale, 1975). By contrast chronic alcoholics and Korsakoff patients, whose thalamic lesions affect the mediodorsal nucleus (experiential working-memory) and spare the ventral anterior nucleus (purposive working-memory), show no deficit of CPT performance (Orzack and Kornetsky, 1966; Mussgay and Hertwig, 1990) or vigilance (Talland, 1965); although like schizophrenics they fail in terms of the

and inserts a new 'set' that is integrated with the connectivity matrix to generate a new 'meaning' as the baseline for working-memory. In the absence of dopamine a plan is difficult to stop, as illustrated by both festination and perseverative errors when performing the WCST. Frontal lobe lesions would impair WCST performance for reasons similar to schizophrenia.
WCST. This supports the suggestion that planning problems added by prefrontal pathology underlie the sustained attention deficit of schizophrenia. As shown earlier (Chapter IV and V) sustained attention also fluctuates with the severity of schizophrenia, whereas WCST appears to be unresponsive to the state.

Further evidence that top-down prefrontal planning processes may be impaired in schizophrenia is provided by neurophysiological findings. Studies of the auditory evoked response potentials (ERPs) to simple physical stimuli normally show a positive deflection between 200 ms and 300 ms post-stimulation termed (P250 or 'P2') that is maximal frontally (Kostandov and D'yachova, 1972; McCarley et al., 1989). The P2 waveform is exogenous and has no emitted counterpart, hence it is unaffected by attention (Alho et al., 1987). The amplitude of P2 is reliably smaller in schizophrenics than in control subjects (Roth and Cannon, 1972; Buchsbaum, 1977; Roth et al., 1980; Faux et al., 1987). Moreover, the reduction was directly correlated to enlargements of the frontal sulcus and rostral interhemispheric fissure (McCarley et al., 1989). The small P2 of the latter study was elicited from schizophrenics as they silently counted infrequent auditory tones (attentive condition). It was considered to represent the primary process of stimulus decoding. However, a different interpretation is suggested by the findings of Chapman, McCrary and Chapman (1978) with healthy subjects. They recorded a positive ERP component at about 250 ms (P2) after a variable digit or letter stimulus (automatic detection) which acted as a template for a later target stimulus. The P2 component was taken to represent the process of storing information in short-term memory. Also, Braff, Callaway and Naylor (1977) observed a reduced auditory P2 when schizophrenics heard a self-initiated stimulus, and attributed the diminished response to a 'very short-term memory dysfunction'. The present interpretation of the ERP results is as follows. The choice of simple physical stimuli allowed rapid stimulus processing by bottom-up construction-integration. Each paradigm also involved an attentive 'set' (purposive context) for the more or less specific target stimuli. The P2 component probably coincided with integration. Attention was paid at the moment of target recognition, coinciding with awareness of the information as it entered experiential working-memory. The time-scale would correspond to that described by Kintsch (1988). The reduced P2 amplitude of schizophrenics suggests less extensive editing of the input, possibly related to a reduced quality of the template (purposive context) used for matching, equivalent to Näätänen's (1990) "attentional trace". The P2 amplitude of schizophrenics correlated

23 Other neurophysiological findings in schizophrenia also provide evidence of a working-memory defects. The reduced P3 amplitude might be explained as for P2, above, but would refer to the subsequent cycle of integration after deeper processing. The reduced contingent negative variation (CNV) amplitude, and its prolongation as the "post-imperative negative variation", might reflect less focussed plans and uncertainty about their resolution due to 'noisy' context in working-memory.
with SADS ratings of delusions and hallucinations (Roth et al., 1980), but also with ratings of negative symptoms McCarley et al. (1989).

A different theory of schizophrenia, which also locates 'memory for context' in the prefrontal cortex, was recently proposed and tested by computer simulation (Cohen and Servan-Schreiber, 1992). The authors refer to a degradation of context that impairs subsequent stimulus processing, similarly hypothesised by Rochester (1978) to explain schizophrenic language deficits. However, context for them is processed, has demands put upon it, has access to knowledge, and deploys attention: "attention can be thought of as the influence that context has on the selection of task appropriate information for processing" (p. 61). The model proposed here restricts 'context' to the contents of working-memory (experiential or purposive context, rather than historical context) and puts attention at the disposition of plans.

4.4 Temporal lobe dysfunction

The model so far has not referred to the role of temporal lobe pathology in schizophrenia, which will now be considered briefly. Prefrontal, limbic, and sensory association cortical fields project in a topographically organized manner to segregated areas of entorhinal cortex (superficial layers: I to III) which relay the input to the hippocampus proper (dentate gyrus and cornu ammonis). The orderly matrix of connectivity within the hippocampus suggests that it might serve as an index for memories located elsewhere in the neocortical and limbic mantle (Teyler and DiScenna, 1985). Return projections from the hippocampus are redirected to the same entorhinal areas (deep layers: IV to VI) as relayed the input, for outward transmission. Reciprocal connections between prefrontal cortex and the hippocampus are necessary to retrieve information that has left working memory, e.g., unfinished parts of a complex plan or information required during the construction phase. A functional link between prefrontal and hippocampal cortices in schizophrenia is suggested by the report (Weinberger, Berman and Torrey, 1992) of a significant correlation between reduced hippocampal volume and decreased prefrontal regional cortical blood-flow (rCBF). Many studies have shown by gross measurement methods that various temporal lobes structures (parahippocampal gyrus, entorhinal cortex, and hippocampus proper) of schizophrenics are smaller than those of healthy subjects (Bogerts, Meertz and Schönfeldt-Bausch, 1985; Brown et al., 1986; Falkai, Bogerts and Rozumek, 1988; Jeste and Lohr, 1989; Suddath et al., 1989; Bogerts et al., 1990; Becker et al., 1992). A smaller volume of the pes hippocampi also discriminated the schizophrenic from the normal twin in a study of monozygotic pairs (Suddath et al., 1990). Cell loss and architectural abnormalities were observed in the entorhinal cortex (Jakob and
Beckman, 1986 and 1989; Falkai and Bogerts, 1992; Falkai, Bogerts and Rozumek, 1988) and in the hippocampus proper (Kovelman and Scheibel, 1984; Jeste and Lohr, 1989; Benes, Sorensen and Bird, 1991). These morphological abnormalities could result in a loss of register between input and output as mapped upon the columns of entorhinal cortex, or other functional impairment. A possible consequence might be that probe cues used to retrieve information from memory would activate material irrelevant to the probe. Such material evoked during the construction process or initiated quite spontaneously might often possess personal significance, since it pertains to past experience. Its location in a well established connectivity matrix might strengthen the material sufficiently to withstand integration with the experiential context, eliciting instead a covert orienting response and causing distraction. Consistent with this interpretation, a diminution of hippocampal volume (dentate gyrus, cornu ammonis and subiculum) as determined by MRI was directly correlated with the severity of positive schizophrenic symptoms (unusual thought content, suspiciousness, hallucinations, and conceptual disorganization), but not with negative symptoms (Bogerts et al., 1992). Whereas the severity of negative schizophrenic symptoms was directly correlated with a reduction of rCBF in prefrontal cortex (Ingvar and Franzen, 1974a and 1974b; Volkow et al., 1987), more florid symptoms were accompanied by an increase of prefrontal rCBF (Hoyer and Oesterreich, 1975; Geraud et al., 1987; Warkentin et al., 1990).

4.5 Aetiology of brain abnormalities

It is often unclear whether the neuropathological abnormalities of schizophrenic brains preceded or followed the onset of illness. The reduced cortical volume of medial temporal lobe structures and increased volume of the temporal ventricular horn in schizophrenics were initially attributed to brain shrinkage of unknown aetiology (Bogerts, Meertz and Schönfeldt-Bausch, 1985; Brown et al., 1986). However, Bruton et al. (1990) by analogy with other maladies regarded congenital malformation as the likely cause of gross abnormalities affecting brain dimensions (reduced brain weight and length, and increased ventricular volume). Also, enlarged ventricles preceded schizophrenic symptoms in two young patients (O'Callaghan et al., 1988; Weinberger, 1988); the ventricular enlargement did not increase with the length of illness (Illoowsky et al., 1988; Roberts, 1990); and was present in young patients and at the first episode of illness (Schulz et al., 1982; Turner et al., 1986; Bogerts et al., 1990). Moreover, the ventricular size correlated with premorbid adjustment (Bogerts et al., 1990; Bruton et al., 1990). The histological abnormalities of schizophrenic brains were considered to be of developmental origin (Kovelman and Scheibel, 1984; Jakob and Beckmann,
A disturbance of neuronal migration in the 4th-5th months of gestation was thought to be genetically induced (Jakob and Beckmann, 1986 and 1989), but an exogenous cause active during the second trimester remains a possibility.

An exclusively developmental and genetic basis to schizophrenia was emphasized by Crow (1993). Evidence for a partial trisomy of chromosome 5 in two related schizophrenics was provided by Bassett et al. (1988). A review by Roberts (1990) also supported a genetic origin, but allowed that environmental causes account for 5-10% of cases. One such cause might be maternal influenza during the second trimester of pregnancy. Influenza epidemics were associated with a subsequent excess of schizophrenia amongst the off-spring exposed in utero (Mednick et al., 1988). The relationship was confirmed by others, and more specifically did not apply to maternal influenza during the first and third trimesters (Mednick, Huttunen and Machón, 1994). Foetal encephalitis caused by tick-bom flaviviruses might account for other cases (Brown, 1994). These virus infections are compatible with the late Winter (Torrey and Bowler, 1990a; Pallast et al., 1994) and urban births of many future schizophrenics (Torrey and Bowler, 1990b). The absence of a reactive gliosis, as would be expected in such cases, may be explained by the immaturity of the immune system at the time of infection, which produces no glial response until after the sixth month of gestation (Roberts et al., 1987).

Hypoxic-ischaemic damage during pregnancy, at birth, or perinatally causes brain abnormalities (dysplasia) similar to the findings for schizophrenia and may be aetiological (review: Murray et al., 1988). Such lesions do not cause gliosis (Windle and Becker, 1944). Focal brain pathology (vascular disease, softening, calcification) was detected significantly more often in schizophrenics than in healthy subjects (especially in the caudate and putamen) and these lesions were correlated with fibrous gliosis (Bruton et al., 1990). Periventricular fibrous gliosis is common (Stevens, 1982) and is unrelated to focal pathology (Bruton et al., 1990). However, the aetiological significance of such pathology is unclear when its time of occurrence is unknown.

The brain abnormalities reported for schizophrenia are various and multiple (David, 1957; Jellinger, 1985; Bruton et al., 1990). Brain pathology at more than one locus is probably necessary to produce schizophrenia and a specific combination of loci may be critical. A single genetic defect expressed at the appropriate stage of gestation may be sufficient to determine the crucial sequelae, but in other cases the same argument might apply to an exogenous cause. Indeed, it is not impossible that genetic and environmental factors must interact to cause yet other cases of schizophrenia (c.f., Murray et al., 1988). All these speculations may be valid if the
final common pathway for a schizophrenic disorder is a particular configuration of anatomical disruption.

Throughout this thesis no distinction has been made between acute and chronic schizophrenia, nor any discrimination between the subtypes of schizophrenia. The analysis of schizophrenic behaviour and the proposed theory appeared sufficiently complicated not to add further complexities. Also, it could not be assumed that the subclassifications of schizophrenia in the cited literature employed identical criteria. Moreover, assumptions of equivalence would be needed, e.g., paranoid = deluded, hebephrenic = nonparanoid = disorganized. Bartko, Carpenter and Strauss (1981) were unable to discriminate hebephrenic from paranoid patients by cluster analyses of 600 patients. Farmer, McGuffin and Spitznagel (1983) obtained a fairly good, but incomplete, separation of hebephrenic from paranoid patients when schizophrenics were analysed by similar methods. However, paranoid and hebephrenic symptoms probably form a continuum (Farmer, McGuffin and Bebbington, 1988), with a transition from the first condition to the second over the years (Tsuang et al., 1981).

5. NEUROLEPTIC EFFECTS

The modifications of neuroleptic therapy reported in Chapters IV and V were partially aimed at validating the PAT as instrument to measure clinical change in schizophrenia. It was not the purpose to investigate the effects of chlorpromazine. Hence this topic will be touched on only briefly.

It was shown recently that midbrain dopamine neurons of monkeys fire phasically in response to salient stimuli, i.e., stimuli with incentive value that attract attention (Ljungberg, Apicella and Schultz, 1991). Behavioural evidence reviewed by Oades (1985) suggested that dopamine promotes the switching of behaviour and the initiation of action (also: Bos and Cools, 1989; Bos et al., 1991). The depletion of dopamine by lesions produced the opposite effects: rats ceased to express a change of motivational state, by no longer switching from one behavioural activity to another (Koob et al., 1978); and rats reverted to 'freezing' (a species-specific behaviour) in preference to the non-naturalistic response of lever-pressing to avoid or to escape electric shock, despite previous training (McCullough, Sokolowski and Salamone, 1993). Hence, switches of attention in schizophrenia might be diminished in a similar manner by a neuroleptic blockade of dopamine transmission, e.g., by acting at inhibitory D2 receptors or excitatory D1 receptors (DiChiara, Morelli and Consolo, 1994); on striatal cells or on inhibitory cortical interneurones (Vincent et al., 1993), respectively.
Chlorpromazine would not be expected to increase task motivation, rather the opposite. Hence the deterioration of PAT performance when the patients received placebo was more likely to be caused by distraction from thoughts and hallucinations, whose relative incentive value increased as task motivation decreased. Dopaminergic input to frontal cortex and the striatum, from the substantia nigra compacta and ventral tegmental area (Bannon and Roth, 1983) facilitates behavioural switching (Oades, 1985). Neuroleptics benefit schizophrenics by a blockade of dopamine D2 receptors (Seeman 1980; Nordström et al., 1993), thus reducing the incentive value of distractors (review: Miller, 1993) and interruptions to the current plan. A greater adherence to plans would increase the amount of information sampled, the feedback of results, and enable better planning.

6 CONCLUSIONS

The attention defect of schizophrenia demonstrated in Chapters IV, V, VI and VIII is caused by intermittent sustained attention as was shown in Chapters VIII and IX. This defect is related to the absolute severity of illness. It responds to chlorpromazine treatment and when the response is sufficient the patients are ready for hospital discharge. Various possible causes of the attention defect were examined in the present chapter. It was argued that attention is deployed by plans which are constantly challenged by rival options. The ‘democratic’ selection of a plan is based upon its ‘value’ and the strength of association between its elements, as compared to rival options. Distraction causes a switch of plan when a rival option is adopted. However, any explanation of schizophrenia based upon the simple notion of greater distractibility was shown to be inadequate. It was necessary to postulate an additional defect, disrupting the mechanism of plan selection, in order to explain the attention defect of schizophrenia.

A mechanism of integration was proposed for plan selection. The model, however, did not discriminate between failures of integration or context as causes of the apparent disintegration. Thus either type of failure could result in a switch of plan. Accordingly, a closer examination of integration was needed in order to identify the origin of impaired attention in schizophrenia. This was undertaken by translating the proposed model of normal cognition into neurological terms. The latter neurological model located integration and context in different structures of the cortico-thalamic basal ganglia circuit. The relevant neuropathology of schizophrenia was reviewed and related to the model. Little or no evidence was found to support the hypothesis of a primary integration failure (striatum). However, a considerable body of data was assembled demonstrating a disruption of neural circuits which
mediate working-memory and context (both experiential and purposive). The relevant cortico-thalamic basal ganglia circuits form loops which return to prefrontal or anterior cingulate cortex. Architectural abnormalities in the cortical segment of these circuits were common, but pathology in other segments of the loops (mediodorsal thalamic nucleus, nucleus accumbens, and globus pallidus) were significant. It was argued that working-memory circuits are modulated (basal ganglia projections to the thalamus) by the latest information resulting from integration (striatum). The thalamic projections are directed to cortical layers III and IV and there coincide with the source of corticocortical projections (layers III, Vb, and VI) which subserve attention. Hence 'meaning' held in experiential working-memory, plans held in purposive working-memory, and the control of attention occupy a single territory. All three functions are impaired in schizophrenia.

Abundant evidence indicates that the hippocampal complex is structurally abnormal in schizophrenia. The extent of this pathology was correlated with the more florid symptoms which comprise first-rank criteria for a diagnosis of schizophrenia. This region is therefore a potential source of potent distractors (e.g., hallucinations and delusions). Their occurrence disrupts sustained attention and causes further symptoms of the illness, but distraction responds well to neuroleptics which prevent a switch of plan. Hence a predominance of positive schizophrenic symptoms may signal a better prognosis. By contrast, pathology involving the prefrontal circuits, described earlier, causes negative symptoms of schizophrenia and fundamental defects of planning and attention. These symptoms respond less to neuroleptics. Hence schizophrenia was classed as an organic psychosis with different aetiologies (e.g., genetic defect, intrauterine infection, perinatal trauma). It remains possible that trauma or disease in later life adds pathology which can transform the illness, e.g., from paranoid to hebephrenic schizophrenia. The observed neuropathology of schizophrenia provides no cause for optimism in terms of a future cure. However, the present results suggest promising applications for new therapies. Attention is central to the schizophrenic syndrome and it varies with the clinical severity of illness. Various patterns of labile attention were observed in the present population of chronic schizophrenics, despite high doses of the neuroleptic. Hence aspects of the underlying defect may be partially functional and in principle treatable.
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APPENDIX I

Patient Demographic Details
## APPENDIX I

### Patient demography (Group I)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at start of study (years)</th>
<th>Chronicity since 1st diagnosis (years)</th>
<th>Institutionalization (years)</th>
<th>Schizophrenic diagnosis at onset of illness</th>
<th>Intelligence</th>
<th>ECT/Insulin treatments</th>
<th>Previous Drugs</th>
<th>Study CPZ</th>
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<td></td>
<td></td>
<td></td>
<td>Prior</td>
<td>Current</td>
<td>Total</td>
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<td>Mill Hill</td>
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<td>95</td>
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<td>16.0</td>
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### APPENDIX I

**Patient demography (Group II)**

<table>
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<th>Patient</th>
<th>Age at start of study (years)</th>
<th>Chronicity since 1st diagnosis (years)</th>
<th>Institutionalization (years)</th>
<th>Schizophrenic diagnosis at onset of illness</th>
<th>Intelligence</th>
<th>ECT/Insulin treatments</th>
<th>Previous Drugs</th>
<th>Study CPZ</th>
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<td></td>
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<td>Mill Hill</td>
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</table>
APPENDIX I

Key

1. Effective IQ assessed by Raven matrices was below the scale limits for nine patients.
2. Exact date uncertain for some patients from other hospitals.
3. Details of admissions to other hospitals not available for some patients.
4. Hospital notes not clear as to courses or treatments of insulin therapy (treatments assumed in table).
5. RTA = road traffic accident.
6. Based upon the literature.