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## Beyond the P300: target and non-target ERP components in schizophrenia

Kerri J. Brown  
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BEYOND THE P300  
TARGET AND NON-TARGET ERP COMPONENTS  
IN SCHIZOPHRENIA

A thesis submitted for the partial fulfilment of the requirements for  
the award of the degree of  
DOCTOR OF PHILOSOPHY IN CLINICAL PSYCHOLOGY

From  
University of Wollongong

by  
KERRI J. BROWN B.A. M.A.  
Department of Psychology

2004

## UNIVERSITY OF WOLLONGONG

## Candidate's Certificate

I, Kerri Brown, declare that this thesis, entitled "*Beyond the P300, target and non-target ERP components in Schizophrenia*", submitted in partial fulfilment of the award of Doctor of Philosophy (Clinical Psychology), In the Department of Psychology, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

Signed: \_\_\_\_\_

Date: \_\_\_\_\_

## TABLE OF CONTENTS

TABLE OF CONTENTS.....	3
LIST OF TABLES.....	5
LIST OF FIGURES.....	6
ACKNOWLEDGEMENTS.....	9
ABSTRACT.....	10
ABBREVIATIONS.....	12
1 INTRODUCTION.....	13
1.1 Rationale and overview of the Thesis.....	13
1.2 Schizophrenia - the clinical picture.....	18
1.3 Genetics.....	21
1.4 Models of schizophrenia.....	24
2 AUDITORY ERPS IN SCHIZOPHRENIA: INTRODUCTION AND RATIONALE FOR STUDY 1.....	30
2.1 Advantages of event related potentials for investigating brain dysfunction in schizophrenia.....	30
2.2 The Fundamental Cognitive Deficit.....	31
2.3 The Oddball Paradigm.....	33
2.4 Auditory P300 findings in schizophrenia.....	34
2.5 Before the P300: target and non-target N100 P200.....	43
2.6 Conclusion.....	51
3 STUDY 1: ERP COMPONENTS ELICITED BY TARGET AND NON-TARGET STIMULI IN SCHIZOPHRENIA AND NORMAL CONTROLS.....	52
3.1 Introduction.....	51
3.2 Hypotheses.....	52
3.3 Method.....	53
3.4 Results.....	57
3.5 Discussion.....	67
4 BACKGROUND AND RATIONALE TO STUDY 2.....	72
4.1 ERPs at first onset of illness vs. chronic schizophrenia.....	72
4.2 Effects of sequential position of non-targets on ERPs.....	82



4.3	Sensitivity of ERPs for schizophrenia .....	85
4.4	ERP Topography in schizophrenia .....	87
4.5	Symptom interactions with ERPs .....	88
4.6	Objectives for Study 2.....	93
5	STUDY 2 - ERPs TO TARGET AND NON-TARGET (BEFORE & AFTER TARGET) STIMULI: FIRST EPISODE VS. CHRONIC SCHIZOPHRENIA .....	95
5.1	Hypotheses .....	95
5.2	Method .....	97
5.3	Procedure and Data Acquisition .....	101
5.4	Analysis.....	102
5.5	Results .....	106
5.6	Discussion .....	163
6	STUDY 3 -ERP SEQUENCE EFFECTS IN FESz 171	
6.1	Introduction .....	171
6.2	Method .....	185
6.3	Data Acquisition .....	187
6.4	Analysis and Results .....	188
6.5	Discussion .....	200
7	STUDY 4 - SPECIFICITY OF TARGET AND NON-TARGET ERP DEFICITS IN FESz COMPARED WITH CLINICAL (ADHD) AND NORMAL CONTROLS 207	
7.1	Introduction and Rationale.....	207
7.2	Method .....	211
7.3	Analysis.....	212
7.4	Results .....	214
7.5	Discussion .....	234
8	THESIS CONCLUSIONS AND IMPLICATIONS .....	239
8.1	Major findings and Implications .....	239
8.2	Limitations and future directions .....	244
8.3	Conclusion .....	246
9	REFERENCE LIST .....	248
10	APPENDICES .....	281

10.1 Appendix 1- Chlorpromazine Equivalent .....	2811
10.2 Appendix 2- Published Papers .....	2822
10.3 Appendix 3- Statistical Summaries .....	CD Rhom

## LIST OF TABLES

Table 2.1 Failure to make use of context in information processing, differing conceptions of a fundamental cognitive deficit. ....	32
Table 3.1 Component means and standard deviations (SD) for control and schizophrenia groups to target and non-target stimuli. ....	60
Table 5.1 Demographic and clinical variables of chronic and FESz participants .....	98
Table 5.2 Medication .....	98
Table 5.3 PANSS items included in each factor .....	103
Table 5.4 Variables entered for N100, P200 DfA.....	104
Table 5.5 N100 and P200 mean and SD for clinical and control groups .....	109
Table 5.6 N200 and P300 Mean and SD to target stimuli for clinical and control groups.....	110
Table 5.7 Summary of the results for N100 amplitude.....	112
Table 5.8 Pearsons two tailed correlations between age and N100 amplitude .....	116
Table 5.9 N100 amplitude correlations with Disorganisation factor. ....	117
Table 5.10 Summary of results for P200 amplitude. ....	119
Table 5.11 Summary of results for P200 latency .....	124
Table 5.12 DfA classification results .....	137
Table 5.13 Summary of results for N100 amplitude.....	140
Table 5.14 Summary of results for P200 amplitude. ....	147
Table 5.15 Summary of results for P200 latency .....	151
Table 6.1 Mean and standard deviation scores for P300 amplitude and latency and N100 components. ....	197
Table 6.2 Mean and standard deviation values for RT. ....	199
Table 7.1 Mean and standard deviation amplitude and latency scores for N100 and P200 components .....	217
Table 7.2 Mean and standard deviation amplitude and latency scores for N100 and P200 components .....	218

Table 7.3 Summary of statistical results for N100 Amplitude .....	220
Table 7.4 Summary of statistical results for P200 amplitude .....	225
Table 7.5 Summary of results for P200 latency .....	229
Table 7.6 Results of discriminant function analyses .....	233

## LIST OF FIGURES

Figure 1.1 A framework for integrating some of the major models of schizophrenia	25
Figure 2.1 Model of the response system in selective attention .....	44
Figure 3.1 Picture of a participant, fitted with the electrocap, in the laboratory. ....	57
Figure 3.2 Between-Group ERP differences for target and non-target stimuli. ....	58
Figure 3.3 Within-group ERP differences for target and non-target stimuli. ....	59
Figure 3.4 N100 amplitude for control and schizophrenia groups, across stimuli, at midline sites and N100 amplitude to target and non-target stimuli, across group, at midline sites .....	61
Figure 3.5 N100 latency to target and non-target stimuli, across sites. ....	62
Figure 3.6 P200 amplitude to target and non-target stimuli at midline sites. ....	63
Figure 3.7 P200 latency to target and non-target stimuli. ....	64
Figure 3.8 P300 amplitude for schizophrenia and control groups at midline sites...	66
Figure 5.1 Average ERPs to target and non-target (T-1& T+1) stimuli, at midline sites, superimposed to show between-group differences. ....	107
Figure 5.2 Average ERPs to target and non-target (T-1 &T+1) stimuli, superimposed to show within subject differences at Cz. ....	108
Figure 5.3 N100 amplitude to target and non-target stimulus at midline sites, by group. ....	113
Figure 5.4 P200 amplitude to target and non-target stimulus at midline sites, by group. ....	120
Figure 5.5 P200 latency to target and non-target stimuli at midline sites for chronic schizophrenia and older controls.....	125
Figure 5.6 P200 latency to target and non-target stimulus in males and females, for chronic schizophrenia and older control groups. ....	126
Figure 5.7 P200 latency to target and non-target stimulus in males and females, for FESz and younger control groups. ....	127



Figure 5.8 N200 amplitude (above) and latency (below) at midline sites for clinical and control groups.	130
Figure 5.9 P300 amplitude at midline sites .....	134
Figure 5.10 N100 amplitude topographical head maps for target and non-target stimulus for clinical and control groups.....	139
Figure 5.11 N100 amplitude to target and non-target stimulus in left and right hemisphere and anterior and posterior regions across chronic schizophrenia and older control groups	
Figure 5.12 N100 amplitude for target and non-target stimulus at anterior and posterior sites in FESz and younger controls. ....	141
Figure 5.13 Topographical head maps for N100 latency to target and non-target stimuli, for control and clinical groups .....	143
Figure 5.14 N100 latency to target and non-target stimulus at anterior and posterior regions .....	144
Figure 5.15 P200 amplitude topographical head maps for target and non-target stimulus for clinical and control groups.....	146
Figure 5.16 P200 amplitude to T-1 and T+1 stimulus for left and right hemisphere and to target and non-target stimulus for anterior and posterior regions across chronic schizophrenia and older control groups and FESz and younger controls	
Figure 5.17 P200 latency topographical head maps for target and non-target stimulus for clinical and control groups. ....	150
Figure 5.18 P200 latency for chronic schizophrenia and older controls across groups for left and right hemisphere (left). P200 latency across FESz and control groups to target and non-target stimulus at left and right hemisphere (right) .	152
Figure 5.19 P200 latency to target and non-target stimulus in anterior and posterior regions. ....	153
Figure 5.20 N200 amplitude and latency topographical head maps for target and non-target stimulus for clinical and control groups.....	155
Figure 5.21 N200 amplitude at anterior and posterior regions. ....	157
Figure 5.22 N200 latency for FESz and younger controls in left and right hemispheres .....	158

Figure 5.23 P300 amplitude and latency topographical head maps for clinical and control groups .....	159
Figure 5.24 P300 amplitude in anterior and posterior regions for FESz and younger control groups. ....	161
Figure 6.1 Grand average ERPs for discontinuation of repetition sequences .....	190
Figure 6.2 P300 amplitude across midline sites (left) and at Pz (right) for DR sequences .....	191
Figure 6.3 Grand average ERPs for the DA series .....	192
Figure 6.4 P300 latency for the two groups as a function of DA series at Pz.....	193
Figure 6.5 Grand average ERPs to continuing and discontinuing sequences .....	195
Figure 6.6 Sequence X Site and Sequence X Stimuli interactions for continuing and discontinuing sequences .....	195
Figure 6.7 RT for DR and DA sequence levels. ....	199
Figure 7.1 ERPs to T-1, Target and T+1 stimulus for normal control, ADHD and FESz groups. ....	215
Figure 7.2 ERP waveforms to T-1, Target and T+1 stimuli, superimposed to show within group differences, for control ADHD and FESz. ....	216
Figure 7.3 N100 amplitude to target and non-target stimuli (T-1 & T+1) for all groups.....	221
Figure 7.4 P200 amplitude to target and non-target stimuli for all groups across midline sites. ....	226
Figure 7.5 P200 amplitude to target and non-target stimuli (T-1 & T+1) for all groups.....	227
Figure 7.6 P300 amplitude for all groups at midline sites. ....	232

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# ABSTRACT

The P300 component of the auditory ERP elicited to target stimuli has been extensively investigated as a potential psychophysiological marker in schizophrenia. Theoretical and empirical evidence is presented, suggesting the earlier components (N100, P200) to both target and non-target stimuli may better capture information processing deficits currently proposed to be central to schizophrenia. The thesis comprises 4 studies.

Study 1 demonstrated deficits to non-target (reduced N100 amplitude, earlier P200 latency), in addition to target stimuli (reduced and earlier N100 amplitude, increased P200 amplitude), in schizophrenia ( $n = 40$ ) compared with matched normal controls. The schizophrenia group was also characterised by a lack of differentiation between ERPs elicited to target and non-target stimuli, in comparison to the normal control group.

Study 2 confirmed the results of Study 1 in groups of chronic (chronic schizophrenia,  $n = 40$ ) and first episode schizophrenia (FESz,  $n = 40$ ), and additionally established that in normal controls non-target stimuli occurring immediately before the target (T-1) generated larger Ni amplitudes than the non-target after (T+1), a pattern that failed to occur in Chronic schizophrenia and was minimal in FESz. N100 amplitude deficits to non-target stimuli were also correlated with clinical symptomatology, particularly with higher levels on the disorganisation factor. Most importantly, N100 and P200 responses to target and non-target (T+1 &

T-1) stimuli, were superior predictors in classifying both first episode and chronic schizophrenia patients than were the more commonly employed P300 measures.

Study 3 examined the effect of certain sequence types on ERPs in FESz ( $n = 14$ ) and normal controls ( $n = 14$ ), in order to ascertain whether P300 and other ERP deficits in schizophrenia could be attributed to impairments on specific sequence occurrences. Specifically, effects from the discontinuation of a long series of repetitions (DR-series) and alternations (DA-series) were examined. In general, patients with FESz demonstrated similar ERPs to controls to the series examined.

Study 4 demonstrated that the early (N100 and P200) component deficits to target and non-target stimuli were *specific* for FESz ( $n = 20$ ), when compared to both a clinical (ADHD,  $n = 20$ ) and normal ( $n = 20$ ) control group. Finally, a stepwise discriminant function analysis (Dfa), demonstrated that measures derived from the early components had better sensitivity and specificity values (vs. N2, P3) for diagnostic classification when compared with ADHD.

This thesis provides compelling evidence that N100 and P200 components to target and non-target stimuli are impaired in both the early and chronic manifestations of schizophrenia, and argues that, on account of the superior sensitivity and specificity values associated with the early components, they may serve as potentially useful biological markers for the disorder.



## ABBREVIATIONS

Abbreviations used in the text throughout this thesis

Abbreviation	Term
ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of Variance
ER_P	Event related Potential
cf.	Compared with
CIDI	Composite International Diagnostic Interview—Computerised Version
CRT	Choice reaction time task
CSz	Chronic schizophrenia
CT	Computer Tomography
DfA	Discriminant function analysis
DA	Discontinuation of alternations
DR	Discontinuation of repetitions
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
FESz	FESz
fMRI	functional Magnetic Resonance Imaging
ISI	Inter stimulus interval;
ITI	Inter target interval
IQ	Intelligence Quotient
MANOVA	Multivariate Analysis of Variance
lVIRI	Magnetic Resonance Imaging
ms	Milliseconds
N	Non-target
n	number
PANSS	Positive and Negative Symptom Scale
PET	Positron Emission Tomography
rCBF	regional Cerebral Blood Flow
RST	Response-stimuli interval
RT	Response Time
SANS	Schedule for the assessment of negative symptoms
SAPS	Schedule for the assessment of positive symptoms
SPECT	Single Photon Emission Tomography
T	Target stimuli
T-1	Non-target stimuli immediately preceding the target stimuli
T+1	Non-target stimuli immediately following the target stimuli
TTI	Target to target interval

*Note.* Abbreviations used in Tables are not given here; all abbreviations will be defined on their first

use in the text.

## 1 INTRODUCTION

### 1.1 RATIONALE FOR AND OVERVIEW OF THE THESIS

The central importance of cognitive deficits to schizophrenia has been proposed for at least a century (Andreasen, Paradiso & O'Leary, 1998; Blueler, 1950/1911; Braff, 1993; Broadbent, 1958; Frith, 1995; Gray, 1998; Hemsley, 1996; Kraepelin, 1989/1919). Although there is little doubt about the existence of a cognitive deficit, the nature of this deficit, its interaction with symptoms, stability over time, whether it follows a neurodevelopmental or neurodegenerative course, and the underlying brain dynamics remain unclear (Andreasen, 2000; Frith, 1992; Goldman Rakic, 1994; Gray, 1998). This primary deficit is seen to underlie impairments in second order cognitive processes (e.g. attention, memory, language emotion) and symptoms of schizophrenia.

The development of event related potentials (ERPs) has provided a window for understanding the neural mechanisms that might underlie this deficit. The millisecond resolution generated by ERPs time-locked to stimuli in cognitive paradigms and recorded over the entire scalp provides a spatio-temporal map of consequent electrical brain activity in the real time of cognition. Understanding the psychophysiology of such a cognitive deficit has exciting implications, in particular the possibilities of identifying a biological validation of diagnosis, an endophenotype for genetic and pharmaceutical research and a biological marker of risk for schizophrenia. The results of this thesis which includes first episode and chronic

schizophrenia participants may also inform treatment intervention and the timing of that intervention and contribute to the understanding of the pathology underlying schizophrenia.

The P300 component of the ERP to target stimuli in the auditory oddball paradigm is seen to reflect "the processing of incoming information when it is incorporated into memory representations of the stimulus and the context in which the stimulus occurs" (Polich & Herbst, 2000, p4). Research has demonstrated a widely reproducible, reduced P300 amplitude in schizophrenia (Ford, 1999; Jeon & Polich, 2000; Pritchard, 1986) which has been suggested as a possible biological marker of risk for schizophrenia (Bharath, Gangadhar, & Janakiramaiah, 2000; Blackwood, 2000; Freidman & Squires-Wheeler, 1994). It has been argued that this reduction represents difficulties in context updating and generation of expectancies (Donchin & Coles, 1988).

There are several limitations in P300 research (see Chapter 2) suggesting the need to look beyond the P300 component. Although reduced P300 amplitude is sensitive for schizophrenia, it is not specific to schizophrenia. Reduced P300 amplitude has also been found in other psychiatric and neurological conditions such as alcoholism (Pfefferbaum, Ford, White & Mathalon, 1991), depression (Pfefferbaum, Wenegrat, Ford, Roth & Koppell, 1984), attention deficit hyperactivity disorder (AMID; Barry, Johnstone & Clarke, 2003), borderline-personality disorder (Blackwood, Sinclair & Kutcher, 1986); Parkinson's disease (Raudino, Garavaglia, Beretta & Pellegrino, 1997) and dementia (Goodin, Squires Henderson & Starr, 1978). In addition, theoretical and empirical findings provide some support for the

notion that a comparator disturbance leading to a failure to make use of context in information processing might occur 100-200ms post-stimulus and consequently would be better captured in the differentiation between target and non-target ERP components, particularly the earlier N100 and P200 components (See Chapter 2.5). ERP studies in schizophrenia have focused mainly on the P300 component elicited by target stimuli, many restricting their analysis solely to P300. Less attention has been given to earlier N100, P200 components to target stimuli and even less to non-target stimuli (see Chapter 2 for review). Hence, it is theoretically compelling and clinically relevant to investigate deficits in earlier components, N100 and P200, to both target and non-target stimuli in schizophrenia. To be valuable, such an investigation would need to demonstrate the presence of these deficits at onset and over longer duration of illness and their improved sensitivity and specificity when compared to the P300.

The thesis is built around four empirical studies and is presented as follows. Chapter 1 provides a brief outline of the thesis, presenting the clinical picture, a review of the symptom structure and major models of schizophrenia. Chapter 2 reviews the previous literature on the auditory P300 component in schizophrenia and presents arguments for the importance of examining ERPs to non-target stimuli in addition to target stimuli. The focus of Chapter 3 (Study 1) is to examine the relationship between the ERPs elicited by target and non-target stimuli in an auditory oddball paradigm. The critical difference between this Study and previous research is the examination of ERP components to non-target in addition to target stimuli, and the examination of the difference in ERP responses to non-target and target stimuli between the schizophrenia and normal control groups.

Chapter 4 reviews and evaluates the literature germane to Study 2, and Chapter 5 describes the Study. This Study encompasses several objectives. In order to exclude the possibility that the deficits identified in Study 1 were a consequence of chronicity, or its many consequences, this Study examines the presence of these deficits in a group of people experiencing their first episode of schizophrenia and their matched control group and contrasts these with deficits found in a group with chronic schizophrenia and their matched controls. The focus is on a more fine-grained analysis of deficits in ERPs to target and non-target stimuli, sub-averaging ERPs elicited by non-target stimuli, depending on their sequence - the non-target occurring immediately preceding ( $T-1$ ) or following ( $T+1$ ) the target stimuli. In addition, the relationship between key symptom clusters and ERP findings are analysed. Although not major objectives of the Study, age and gender effects were also briefly examined. The wide age span arising from this design allows for a comparison of age effects between schizophrenia and normal control groups. Gender differences in schizophrenia have recently gained theoretical relevance and hence differential gender effects on ERPs between clinical and control groups are also investigated.

The interpretation of Study 2 results led to questions regarding sequence effects on ERPs to target and non-target stimuli in schizophrenia, necessitating the development of a different paradigm. These questions were investigated in Study 3 (Chapter 6). The improved sensitivity for schizophrenia of N100, P200 components elicited by target and non-target stimuli versus N200 and P300 to target stimuli also

lead to a further investigation of the relative specificity of these components in Study 4 (Chapter 7).

Chapter 6 introduces and describes Study 3. This Study examined how sequence effects on ERPs may contribute to an understanding of difficulties with either the independent processing of target and non-target stimuli and/or the interrelated processing of these two stimuli in a group with first episode schizophrenia. The Study focuses on the effects of the discontinuation of alternation sequence on P300 amplitude, latency and RT, as a possible index of associative strength. A further aim of this Study was to discriminate between two competing hypotheses emerging from the results of Study 2 regarding the absence of sequence effects on the non-target N100 amplitude in schizophrenia.

The final experimental Study (Study 4) is described in Chapter 7 and examines whether deficits in N100 and P200 components to target and non-target stimuli, observed in chronic and first episode schizophrenia were specific to this disorder. As ADHD shares deficits in common cognitive domains (eg. attention, working memory and inhibitory dysfunction) with schizophrenia (Chapter 7.1) they provide a useful psychiatric control group for exploring the specificity of ERP findings in schizophrenia, particularly in a young group with FESz. Hence, Study 4 examined ERPs to target and non-target stimuli (T-1 & T+1) in FESz in comparison to normal and psychiatric (ADHD) control groups.

Chapter 8 comprises a summary, interpretation and discussion of the four studies previously conducted. The theoretical and clinical implications are also discussed, as are the limitations of this thesis and suggestions for further research.

In summary, this thesis significantly contributes to ERP findings within the schizophrenia literature and enhances the theoretical understanding of the mechanisms that may contribute to the psychopathology of this clinical condition.

## 1.2 SCHIZOPHRENIA - THE CLINICAL PICTURE

### 1.2.1 Classification and course

There is, as yet, no accepted biological validation for the diagnosis of schizophrenia, which is a clinical diagnosis based upon the evaluation of reported and observed symptoms (Sedvall & Terenius, 2000). Diagnosis is made on the basis of characteristic positive (delusions, hallucinations, disorganized speech or behaviour) and negative (affective flattening, alogia and avolition) symptoms, with continuous signs of disturbance for at least six months. These symptoms are accompanied by deteriorating personal, social and occupational functioning and are not secondary to another disorder e.g. substance abuse (American Psychiatric Association, 1994). The peak age of onset is in the twenties, with onset generally a little earlier in males than females (Hafner et al., 1998). Schizophrenia is one of the most costly mental illnesses in terms of its impact on patients, their families, the health system and the economy (Langley-Hawthorne, 1997; Andreasen, 1995). Schizophrenia has a range of courses and outcomes (Gaebel & Frommann, 2000). Although onset may be abrupt the majority of individuals display some type of prodromal phase which may last a year or more before the onset of overt psychotic symptoms. Although Kraepelin (1889/1919) conceived dementia praecox as a deteriorating illness, Bleuler (1908/1911) emphasized that the course could be

irregular with remissions and intermediate outcomes. Ciompi (1988) suggests the course of schizophrenia is not always catastrophic, as almost 30% of patients can get well or have a good remission and in 30% a mild residual symptomatology persists. DSM IV (American Psychiatric Association, 1994) specifies six main course patterns: episodic with interepisode residual symptoms, episodic with no interepisode residual symptoms; continuous, single episode in partial remission, single episode in full remission and other or unspecified.

Schizophrenia has a similar clinical presentation and prevalence throughout the world, a lifetime and point prevalence of approximately 1 percent (Sartorius, Jablensky & Korten, 1986). However, sex differences have been reported with a two to three-fold increase in the incidence of schizophrenia in males (Hambrecht et al., 1994; Timms, 1998). Compared with females males have been found to show poorer premorbid adjustment (Childers & Harding, 1990; Salokangas, 1983), younger age at onset and at first hospitalization (Hafner et al., 1989; Loranger, 1984; Shtasel, Gur, Gallacher, Heimberg, & Gur, 1992), more severe symptoms and course of illness (Angermeyer, Kuhn, & Goldstein, 1990; Childers & Harding, 1990; Goldstein, 1988; Goldstein, Santangelo, Simpson, & Tsuang, 1990; McGlashan & Bardenstein, 1990; Salokangas, 1983) worse social and vocational outcome (Childers & Harding, 1990), greater structural brain anomalies (Gur et al., 2000; Harvey et al., 1990; Leong & Chue, 2000) and neurological soft signs (Alexander et al., 1994).

### 1.2.2 Clinical heterogeneity

Schizophrenia has been considered a heterogeneous disorder in terms of both clinical symptoms and neuropathological findings (Hemsley, 1996). One approach to



explore this heterogeneity has been the use of categorical subtypes for example, paranoid/non paranoid (Kremen, Seidman, Goldstein, Faraone & Tsuang, 1994), thought disorder/no thought disorder (Tallent, Weinberger & Goldberg 2001), positive/negative (Crow, 1980) or deficit/non-deficit (Carpenter, Heinrichs, & Wagman, 1988). However one problem with this approach is that individual patients may have symptoms from more than one category, for example, many patients with schizophrenia exhibit both positive and negative symptoms. An alternative approach uses factor analysis to reduce the large number of symptoms into factors that can co-occur in individual patients.

Many factor analytic studies (Andreasen, Arndt, Miller, Flaum & Nopoulos, 1995; Liddle, 1987; Loftus, DeLisi, & Crow, 1998) suggest that three primary symptom factors account for the interrelationships among the core symptoms of schizophrenia. The three factors have been characterised by Liddle (1987) as follows: (1) psychomotor poverty - deficit negative symptoms such as affective flattening, emotional and social withdrawal, and avolition); (2) reality distortion - positive symptoms of hallucinations and delusions; and the (3) disorganisation factor - positive and negative aspects of thought disorder and attentional problems. These studies have largely limited factor analysis to the core symptoms of schizophrenia as measured by the schedule for the assessment of positive symptoms (SAPS), and the schedule for the assessment of negative symptoms (SANS, Andreasen, Arndt, Miller, Flaum & Nopoulos, 1995) or the positive and negative sections of the positive and negative syndrome scale (PANS S, Kay & Opler, 1987). When investigators have added symptoms of general psychopathology to the factor analysis (usually the

psychopathology section of the PANSS), they have found that five factors, or more, are necessary to explain the heterogeneity of symptoms in schizophrenia (Bell, Lysaker, Beam-Goulet, Milstein, Lindenmayer, 1994; Lancon, Reine, Llorca, Auquier, 1999; Lindenmayer, Grochowski, & Hyman, 1995). In these studies the three core factors have largely remained, with the addition of two or more further factors, although the exact symptoms that comprise these dimensions differ slightly across studies. The two most common additional factors have been characterised as excitement and depression/anxiety. Consideration of symptom factors can unlock significant associations with brain function that can be obscured through traditional group averaging (Harris, Williams, Gordon, Bahramali & Slewa-Younan, 1999; Liddle, 1987, 1992; Liddle et al., 1992; Williams, Gordon, Bahramali, Wright & Meares, 2000). For example, Harris (2004) found increased alpha 2 and beta power associated with reality distortion (divided into psychotic and paranoid domains) while finding decreased alpha and beta power associated with the disorganisation factor. A review of the relationship between symptom factors and cognitive domains, psychophysiology and imaging factors is presented in Chapter 4.4

### 1.3 GENETICS

Evidence from many studies demonstrates that genetic factors contribute substantially to the aetiology of schizophrenia (Gottesman, 1991; Moldin & Gottesmann, 1997) with epidemiological studies suggesting that additive and interactive genes, each with small effects, mediate this genetic vulnerability (Joober, Boksa, Benkelfat, & Rouleau, 2002). Genetic research has led to the questioning of the usefulness of the DSM IV categorical definition of schizophrenia for genetic

investigation, while acknowledging its necessity for clinical purposes. The disorder is unlikely to be caused by one gene that is 100% penetrant and the number of people that meet the requirements of DSM IV may be only a selected fraction of the total occurrence of the phenotype (Clonninger, 1994). Strauss (1969) and others (Claridge, 1994; Johns & Van Os, 2001) have suggested that psychosis may exist as a continuous phenotype in nature. Phenotype incorporates the observable characteristics of an organism in contrast with genotype, which is an organism's genetic composition

The most widely accepted model for the transmission of schizophrenia, the polygenic threshold model (Gottesman & Moldin, 1997; Gottesman & Shields, 1967) proposes that the liability to develop the disorder is normally distributed in the population, reflecting the additive effects of several different genes plus environmental factors. Thus, only those individuals who exceed a certain threshold of liability would develop the disease. Relatives of schizophrenic patients have, on average an increased liability compared with the general population because of predisposing genetic factors, causing more of these relatives to be beyond the threshold for manifesting the disorder. The strongest evidence for the existence of schizophrenia susceptibility loci has been found on chromosomes 1, 6, 8, and 13 (Bailer, et al., 2000; Brzustowicz et al., 2000; Gurling et al., 2001; Schwab et al., 2000 Shaw et al., 1998 Williams et al., 1999). However, statistical evidence is not strong, and the existence of nonreplications demonstrates that these findings are not conclusive (National Institute of Mental Health's Genetic workgroup, 1999).

The problems surrounding the adequacy of the current diagnostic criteria for schizophrenia, and the heterogeneity of individuals currently classified, contribute to the importance of identifying biological endophenotypes, as they can identify relatives of affected individuals who would be considered unaffected with typical diagnostic systems. They can also identify individuals at risk before the development of the disease and help to identify a candidate location for illness-susceptibility loci (Porjesz et al., 2002). Endophenotypes represent measurable characteristics that reflect an underlying genotype that may be more closely related to that genotype than the diagnostic category itself. Endophenotypes must be associated with the illness in the population, heritable, primarily disorder dependant and co-segregate with illness within families (Gottesmann & Gould, 2003). The heritability of P300 amplitude in the normal population has been estimated around 60% (van Beijsterveldt & van Baal, 2002; Wright et al., 2001) with highest heritability (79%) from the Minnesota twin sample (Katsanis, Iacono, Mcue & Carlson, 1997). Very few studies have looked at the heritability of the N100 and P200 components. Studies which have included N100 have found both amplitude and latency heritable (Koutchoubei, 1987 - orienting task; O'Connor, Mozerati, & Christian, 1994 - oddball; Surwillow, 1980 - oddball). O'Connor et al. also found genetic influences in the waveform shape of ERPs to both target and non-target stimuli. There are few studies that link ERPs to genetic findings in schizophrenia. Blackwood (2001) has linked P300 amplitude to chromosome 1. Preliminary findings about the heritability of target and non-target ERP components suggests their potential as endophenotypes is worthy of further investigation.

#### 1.4 MODELS OF SCHIZOPHRENIA

The last one hundred years of schizophrenia research has shown a shift from viewing schizophrenia as a loosening of association *cognitively* (Blueler, 1950/1911) and a neurodegenerative view of its course (Kraepelin, 1896), to a focus on specialised or focal deficits, and then to a *biologically* driven focus on disconnection and a neurodevelopmental hypothesis (Bullmore, Frangou, & Murray, 1997; Friston, 1998; Peled, 1999). Figure 1 is an attempt to integrate some of the major models with a unified cognitive deficit and pathophysiology into a working model of schizophrenia.

Comprehensive models of schizophrenia need to account for multiple aetiologies including genetic contribution, the age of onset, its remitting and relapsing course, the modulating role of neurotransmitters, the heterogeneity of symptoms and the difficulty in finding a pathophysiological marker. The stress-vulnerability model of schizophrenia (Zubin & Spring, 1977; Nuechterlein & Dawson, 1984; Clements & Turpin, 1992) provides insight into the remitting and relapsing course of schizophrenia. This model proposes that a predisposition to schizophrenia on the basis of genetic vulnerability and ecogenetic effects interacts dynamically with psychosocial factors in the individual's life such as family environment, social network and substance abuse to establish a threshold, beyond which a person may develop schizophrenia or psychosis. This threshold moves as protective or destructive factors intersect with the person's vulnerability.

## Working Model of Schizophrenia

### (A) Etiology: multiple convergent factors

DNA, gene expression, viruses, toxins, birth injury, psychological experiences



Dysplasia during second half of gestation (resulting in abnormal asymmetry and connectivity of the adult brain); abnormal synaptic pruning at adolescence.

(C) Anatomic and functional disconnection in neuronal connectivity and communication in the mature brain involving the modulation of long-term changes in synaptic efficacy by the ascending neurotransmitter systems.



### (D) Impairment in a fundamental cognitive process

A breakdown in the normal relationship between stored material and current sensory input or failure to make use of context in information processing  
(See Chapter2, Table 2.1)



(E) Impairment in one or more second order Cognitive Processes  
(E.g. attention, memory, language emotion)



### (F) Symptoms of Schizophrenia

(Reality distortion, psychomotor poverty, disorganisation, excitement and depression/anxiety)

Figure 1. 1 A framework for integrating some of the major models of schizophrenia  
Note. Figure adapted from Andreasen's (2000, p108) working model. Changes to Andreasen's model are in blue. Arrows in blue have been made bidirectional to reflect the possibility of a two rather than one way interaction.

The disconnection model, suggesting that different neuronal systems in the brain have become disconnected from each other in schizophrenia (Friston 1998, 1999) has provided the stress-vulnerability model with a plausible pathophysiological mechanism. Research suggests that perhaps the difficulty in finding a single pathophysiological marker despite many years of research is because the pathology in schizophrenia may involve multi-distributed neural circuits and neurotransmitter systems (Andreasen, Paradiso, & O'Leary, 1998; Bullmore, et al., 1997; Friston, 1999; Goldman Rakic & Selemon, 1998; McGlashen & Hoffman, 2000; Peled, 1999). Disconnection models have been proposed in different, but generally compatible versions by several proponents.

Friston (1999) proposes a regionally specific disruption of effective connectivity within the brain through experience, or activity dependent plasticity in systems which would only be functionally expressed in the developed brain, involving ascending modulatory neurotransmitters. The reduced neuropil hypothesis (Selemon & Goldman-Rakic, 1999) proposes that the reduction of interneuronal neuropil in the prefrontal cortex is a prominent feature, and suggests a major role for prefrontal regions and their multiple distributed cortical, thalamic and striatal connections in schizophrenia. Peled (1999) suggests a disorder of multiple constraint organisation with specific symptom factors determined by the site and level of the disconnection. Reality distortion is associated with a breakdown in auditory unimodal networks and their connections with heteromodal networks, psychomotor poverty is associated with disturbances in constraint satisfaction of the networks located at the highest levels of the hierarchy, and disorganisation is associated with disturbance that encompasses most if not all brain systems.

Disconnectivity models can also account for the timing of the onset of schizophrenia through neurodevelopmental hypotheses. These hypotheses argue that there are two stages in the development of the brain that can be linked to brain abnormalities that lead to schizophrenia. The first period, the early neurodevelopmental stage, takes place during the pre-natal and neonatal period. It is argued that a combination of early brain lesions and environmental factors such as pre-natal viral infections, obstetric complications and winter or early spring births may combine together to predispose a person to schizophrenia but that frank psychosis may not occur until the brain has matured sufficiently. For example, Bullmore et al. (1997) present evidence that dysplasia during the second half of gestation would result in abnormal asymmetry and connectivity in the adult brain.

The next period, the late neurodevelopmental stage, is thought to take place during brain maturation. Here it is argued that schizophrenia may develop as a consequence of abnormal synaptic pruning occurring during adolescence. Loss of synaptic density is known to be a feature of neurodevelopmental plasticity, with upwards of 60% of synapses being pruned in normal CNS development. This process reaches the prefrontal and association areas relatively late in the developmental course during mid-adolescence (Huttenlocher & Dabholkar, 1997), at the same time as the period of greatest risk for schizophrenia. An acceleration of this process of synaptic loss may underlie the expression of schizophrenia at this stage as well as the substantial cortical grey matter volume loss in the longitudinal structural magnetic resonance imaging (sMRI) studies of recent onset schizophrenia (DeLisi et al., 1997; Rapoport et al., 1999; Lieberman et al., 2001).



Evidence in support of disconnection models has been found in different modalities. Several investigators (Woodruff et al., 1997; Bullmore et al., 1998; Wright et al., 1999) argue that areas that share neurodevelopmental influences develop in parallel, establishing statistically definable structural interdependencies that reflect continued connectivity. Structural MRI studies have identified these dependencies in normal controls, however decreased interregional dependencies particularly between frontal hippocampal and temporal regions have been found in people with schizophrenia (Woodruff et al., 1997; Bullmore et al., 1998; Wright et al., 1999). Studies have also shown low neuropil levels (Lewis et al., 1999) abnormalities in synaptic, dendritic, axonal, and white matter tract organization, and abnormalities of glutamatergic neurotransmission, (Garey et al., 1998; Glantz & Lewis, 2000; Goldman Rakic & Selemon, 1997) which are consistent with disturbed intracortical connectivity.

It is also possible that disconnectivity is anatomically restricted, rather than widespread, with certain cortico-cortical and cortical-subcortical connections particularly vulnerable to disruption in schizophrenia. The strongest evidence to date has emphasised the disconnectivity between frontal and lateral temporal cortices (Frith et al., 1995), between the frontal cortex and the hippocampus (Weinberger, Berman & Torrey, 1992); and in both fronto-striatal thalamic (Robbins, 1990) and in fronto-thalamic-cerebellar (Andreasen et al., 1998) circuits. Gray (1995, 1998) proposes a specific disconnection, an anatomic abnormality in the limbic forebrain, affecting the hippocampal formation, amygdala and temporal and frontal neocortex, leading to a functional neurochemical abnormality, hyperactivity of transmission in the ascending mesolimbic dopaminergic pathway, that disrupts the comparator

process. The comparator "has the general function of predicting, on a moment by moment basis, the next perceived state of the world, comparing this to the actual next perceived state of the world, and determining whether the predicted and actual states match or mismatch" (Gray 1995, p 680).

The point of entry for this thesis is at level D (see Figure 1.1) the psychophysiology of the fundamental cognitive deficit - a breakdown in the normal relationship between stored material and current sensory input or the failure to make use of context. However, there is also interaction with other levels, for example, E - resultant cognitive deficits; F - clinical symptoms; and at levels prior to D, if the determined deficits are shown to have potential as biological markers for genetic investigation.

## 2 AUDITORY ERPs IN SCHIZOPHRENIA: INTRODUCTION AND RATIONALE FOR STUDY 1.

### 2.1 ADVANTAGES OF ERPS FOR INVESTIGATING BRAIN DYSFUNCTION IN SCHIZOPHRENIA

Neuroimaging technologies for investigating brain dynamics in schizophrenia include electroencephalogram (EEG), event-related potentials (ERP), positive emission tomography (PET), functional magnetic resonance imaging (fMRI), and single photon emission computerized tomography (SPECT). Although PET, SPECT and fMRI, provide good spatial resolution, these methods do not have the temporal resolution to investigate cognitive processing in the millisecond domain (Gordon, 2002). Andreasen, Nopoulos, O'Leary, Miller, Wassink and Flaum (1999) claim that "the rapid constant checking and updating of input and output" occurs "at the nanosecond level" (p. 911). While the claim for nanoseconds may be taking poetic license with the physiology of nerve action potential, it nevertheless points to the advantages of a technique such as the event related potential (ERP) which has millisecond resolution.

ERPs provide an index of electrical brain activity time-locked to sensory stimuli and provide a spatiotemporal map of consequent neural events. They are also able to distinguish processing stages and can clarify the timing, ordering and interactions of the intermediate processes that are engaged in specific cognitive activities (Hillyard & Kutas, 1983). An advantage of ERPs is that neural responses can be measured for all stimuli, regardless of whether an overt response is required. This makes ERPs ideally suited for the purpose of this Study as they allow us to assess the extent to which non-targets, which do not require a response are processed.

In contrast measures of performance such as response time (RT) are less able to focus on brain activity to non-target stimuli. Additionally, the analytic requirements of NMI i.e. subtraction of the baseline activation, elicited by non-target stimuli from the activation elicited by target stimuli also make it difficult to examine and contrast early (pre N200 & P300) brain activity to target and non-target stimuli. Several studies have shown a robust within subject test-retest reliability for ERP components supporting their validity as markers of CNS functioning (Sandman & Patterson, 2000; Segalowitz & Barnes, 1993; Sinha & Parsons, 1992; Walhovd & Fell, 2002). Results from these studies have indicated that measures of amplitude show superior reliability over measures of latency. Other advantages of ERPs are that they are accessible and non-invasive. Thus ERPs are well suited to the investigation of cognitive deficits in schizophrenia and particularly to the investigation of the proposed comparator disturbance.

## 2.2 THE FUNDAMENTAL COGNITIVE DEFICIT IN SCHIZOPHRENIA

While the capacity to ignore task irrelevant stimuli and optimally process relevant target information is seminal to normal brain function, early models of cognitive disturbance in schizophrenia suggested a global failure of this process, commonly associated with filter disturbances (Broadbent, 1958). Recent models (Gray, 1998; Gray, Feldon, Rawlins, Hemsley and Smith, 1991; Hemsley, 1996) propose a core physiological mechanism underlying this process, namely a disturbance of the comparator process. The Gray-Hemsley model proposes that the cognitive deficits exhibited by patients with schizophrenia correspond to a breakdown in the normal relationship between stored material and current sensory input. Thus, people with schizophrenia fail to establish appropriate response biases

because they are unable to use stored memories of regularities based on their previous experience. This model is consistent with Sokolov's (Sokolov, 1963; Sokolov & Vinograda, 1975) neuronal model, and with aspects of the models proposed by Andreasen et al. (1998), Frith (1995), and Servan-Schreiber, Cohen, and Steingard (1996), suggesting a deficit in the co-ordination and expression of information, a disruption in the monitoring of willed intention, and a failure in the inhibitory effect of context, respectively. The fundamental cognitive deficit could thus be seen as a failure to make use of context in information processing Table 2.1).

Table 2.1 Failure to make use of context in information processing, differing conceptions of a fundamental cognitive deficit.

"It is a weakening of the influence of stored memories of regularities of previous input on current perception" (Hemsley, 1987, p182). "This stored body of knowledge normally interacts with the encoding, comprehension and or retrieval of new information by guiding attention expectancies, interpretation and memory search." (Hemsley, 1996)

A disturbance of the comparator process which "has the general function of predicting, on a moment by moment basis, the next perceived state of the world, comparing this to the actual next perceived state of the world, and determining whether the predicted and actual states match or fail to do so ("mismatch")". (Gray, 1995, p 680)

"Several schizophrenic deficits could be related to a disturbance in a single mechanism with pervasive implications for cognition: the representation and maintenance of context information". (Servan-Schreiber et al., 1996, p 1105)

"An impairment of the neural mechanisms by which symbolic representations are both retrieved from long-term memory and 'held in mind' to guide behaviour in the absence of instructive stimuli in the outside world" (Goldman-Rakic & Seleman, 1997, p 437-438)

A disorder of consciousness or self awareness that impairs the ability to think with "metarepresentations" (higher order abstract concepts that are representations of mental states) (Frith, 1992)

Cognitive dysmetria "a disruption in the fluid co-ordination of mental activity that is the hallmark of normal cognition... The basis of the poor co-ordination may be a defect in timing or sequencing the flow of information" (Andreasen et al., 1999, p 911)

### 2.3 THE ODDBALL PARADIGM

The auditory oddball paradigm, also called the P300 paradigm, is one of the earliest and most extensively researched paradigms for eliciting cognitive ERPs (Ford, 1999; Picton, 1992), with a body of evidence on functional and clinical implications. In the 'oddball' paradigm, a subject detects and responds to an infrequent but task-relevant stimulus (target), randomly interspersed among more frequent, standard stimuli (non-target). These stimuli can be either auditory or visual. Most studies in schizophrenia have reported the auditory, rather than the visual P300 (Ford, 1999) as P300 abnormalities are more consistently observed in auditory paradigms (Egan et al., 1994; Ford et al., 1994; Pfefferbaum, Ford, White & Roth, 1989). In the auditory version of the oddball paradigm, the participant is instructed to listen to a series of high and low tones, and to respond (e.g. by button press or counting) to one tone designated the target stimuli. There is thus a string of frequently occurring stimuli (standards or non-targets) interrupted intermittently by infrequently occurring (rare or target) stimuli, making the non-targets the context in which the decision 'target' is made. This comparison between target and non-target stimuli has been likened to the comparator process (Ford, 1999; Brown, Gonsalvez, Harris, Williams, & Gordon, 2002). Kok (1997) suggests that the primary function of the neural network involved in target identification in the oddball is to compare stimulus attributes with an internal representation of the target, or memory-dependant characteristics of the target. Although more sophisticated paradigms exist for examining the use of context and selective attention, they are often too complex to use in clinical settings. As generalised attentional and/or motivational impairments adversely affect performance on most cognitive tasks in schizophrenia, it is important to have a task that patients are capable of performing and that does not require training. The

auditory oddball has the advantage of being a simple task which can be performed by most subjects. Thus an ERP deficit elicited by such a task is likely to reflect mechanisms implicated in the processing requirements of the task, rather than secondary reactions to the level of difficulty or incorrect performance on the task. Notably, a disturbance at this level may underpin disturbances found in more complex paradigms. A review of P300 findings in schizophrenia, indicates the contribution the oddball paradigm has made to our understanding of the cognitive disturbance in schizophrenia, along with the limitations of this research, and some questions that arise from it.

#### 2.4 AUDITORY P300 FINDINGS IN SCHIZOPHRENIA

Roth and Cannon (1972) and Levitt, Sutton and Zubin (1973) were the first to use the auditory oddball paradigm with people with schizophrenia, both finding reduced P300 amplitude to target stimuli. These studies utilised the oddball paradigm in the *passive* condition, where subjects ignore the tones. Most subsequent studies have used the *attend* paradigm, where subjects either count or press a button to targets. Roth and Cannon's study is particularly relevant, as it was the only study found which examined the non-target before and after the target stimuli separately, in schizophrenia, apart from the Studies 2 and 4 in the current thesis.

The P300 deficit has been reproduced widely (Ford, 1999; Jeon & Polich, 2000; Pritchard, 1986) making it "perhaps the most replicable biological reflection of schizophrenia" (Ford, 1999, p 668). Most oddball studies have concentrated on the P300 component to the target stimuli, as the P300 component was seen as

endogenous, or sensitive to cognitive determinants. The earlier components, N100 and P200 which occur in both target and non-target stimuli, were seen to be more exogenous, or sensitive to manipulations of sensory characteristics (Van Der Stalt, 1999). The interpretation of the reduced P300 in schizophrenia has led to a number of hypotheses which have generated a large area of research. Important issues arising from this research are explored below.

#### 2.4.1 Neuroleptic medication and P300

A common limitation of many P300 studies in schizophrenia is the use of medicated patients as subjects. As untreated psychosis has undesirable outcomes, both in the short and long term, withdrawing a patient from medication or delaying the introduction of medication raises important ethical questions. However, the possibility that medication may influence ERP findings needs to be considered. As it is a variable occurring in the clinical and not in the control group, it is necessary to demonstrate that the differences between groups are not attributable to medication. This is especially important, as several neuroleptic medications also have anticholinergic effects, and specific anticholinergics are used to control extrapyramidal symptoms. However, cholinergic suppression has been shown to reduce P300 amplitude in healthy individuals (Hammond, Meador, Aung-Din, & Wilder, 1987; Meador et al 1987; Meador et al 1988 and Meador et al 1989).

The possibility that reduced P300 in schizophrenia could be a medication artefact has been addressed by several studies which have found reduced P300 in patients with schizophrenia who have been withdrawn from neuroleptic medication



(Coburn et al., 1998; Ford et al., 1994; Laurent et al., 1999; Ogura et al., 1991) and in a neuroleptic—naïve sample (Hirayasu et al., 1998).

More recently, several studies have examined the interaction of medication and P300 from the alternative view, the possibility that neuroleptic medicine could normalize the P300 reduction in schizophrenia. While traditional antipsychotic medications do not appear to increase P300 amplitude in schizophrenic patients (Blackwood et al., 1987; Ford et al., 1994), there have been mixed results with the atypical antipsychotic medications that target various subtypes of serotonin receptors and D4, rather than the D2 dopamine receptors targeted by typical antipsychotic medication. Clozapine has been reported to increase P300 amplitude (Umbricht et al., 1998), while risperidone had no significant effect on P300 amplitude but normalized the latency (Iwanami et al., 2001). Gonul et al. (2003) found that, although olanzapine normalized P300 amplitude over the frontal area, the effect was unrelated to changes in the patients' clinical symptoms, and P300 amplitude over the parietal area remained below normal limits. The salient point here is that reduced P300 amplitude in schizophrenia does not appear to be the consequence of antipsychotic medication.

#### 2.4.2 Effects of probability manipulations on P300 deficits in schizophrenia

Although there is a large body of work on the effects of probability and local sequence effects on the P300 in the normal population, this area received little attention in schizophrenia research. The bulk of studies on P300 in schizophrenia have used low probability targets (Jeon & Polich, 2000). Duncan, Perlstein and

Morihasa (1987) varied probability (0.10, 0.30 and 0.50) and found that patients with schizophrenia had significantly reduced P300 only to low probability stimuli. Mathalon and Ford (2002) varied probability between 0.2 and 0.8 and again found a significant reduction in P300 amplitude only to the low probability stimuli in schizophrenia. However the results in both these studies could be due to target to target interval (TTI) (see Chapter 6 for review of TTI versus probability) rather than probability. Sequence effects in schizophrenia have received even less attention, with only one study on sequence effects on P300 and RT in schizophrenia (Duncan-Johnson, Roth and Kopell, 1984). This Study used a choice reaction time task which requires a response to all stimuli presented. No studies were found which investigated sequence effects on ERPs elicited by the non-target stimulus, or to target stimuli which occurred amongst stimuli which did not require a response. There is thus a need for further investigation of the effects of stimulus sequence on ERPs elicited by target and non-target stimuli in schizophrenia. The literature on sequence effects on ERPs is discussed in more detail in Chapter 6 in which Study 3 examines sequence effects on ERPs to target and non-target stimuli in FESz.

#### 2.4.3 Interstimulus Interval (ISI) and P300 in schizophrenia

ISI is another variable demonstrated to influence the magnitude of P300 amplitude. Studies have shown that P300 amplitude is not reduced in schizophrenia in comparison with normal controls in paradigms with long ISIs (Mathalon & Ford, 2002; Roth, Goodale & Pfefferbaum, 1991). Mathalon and Ford examined the differences between short (1.5 secs) and long (8 sec) ISI and found that with the increase in ISI controls showed a slight decrease in P300 amplitude to targets but a

marked increase in P300 to standards. In contrast, patients with schizophrenia showed no change in the P300 to targets and a relatively small increase in P300 to standards with the ISI increase. Relative to the controls, P300 amplitude to targets was reduced in the schizophrenic patients with the short but not the long ISI. Without non-targets (standards) there is nothing with which to compare the target making limited demands on comparative or working memory processes (Donchin and Coles, 1988). Ford (1999) suggests that whether P300 amplitude differs between schizophrenia and normal controls, depends on either the absence of a comparator process, i.e. where there is only the target and no non-target, or a very long ISI.

#### 2.4.4 Skin conductance and P300 in schizophrenia

Some investigators have attempted to explore the relationship between skin conductance and P300. The main difficulty in these attempts was that the P300 is recorded in an attend paradigm usually with ISIs of a few seconds, while SCRs, which have recoveries over tens of seconds, are usually acquired in an ignore paradigm, with much longer ISIs. Roth, Goodale and Pfefferbaum (1991) attempted to explore the interaction of P300 and skin conductance in a passive three stimulus oddball and an active one stimulus reaction task with interstimulus intervals greater than 12 seconds. Not surprisingly, and consistent with findings that the P300 is not reduced in schizophrenia with experiments employing longer ISIs (Mathalon & Ford, 2002), they did not find a reduction in P300 in schizophrenia. The development of a program to decompose the overlapped SCRs collected in a short ISI paradigm (Lim et al., 1997) allowed the simultaneous collection of SCRs and ERPs in the traditional short ISI P300 paradigm. Williams et al. (2003) subaveraged ERPs based on the

presence or absence of an SCR defined orienting response (OR), and found that the pattern of increased frontal P300 in the 'with OR' compared to the 'without OR' condition present in the control group, was not found in the group with schizophrenia. These results indicate that P300 may be modulated by arousal.

#### 2.4.5 Single trial studies of P300 in schizophrenia

As P300 amplitude reduction in schizophrenia had been demonstrated in ERPs averaged across the experiment, it was possible that the averaging process may be obscuring variability within the ERPs elicited by individual targets. Ford, White, Lim & Pfefferbaum (1994) applied a P300 screen to all single trial responses to target stimuli and found that the schizophrenia group had fewer trials passing the P300-screen, smaller P300s on each trial, and P300s that were more variable in latency across trials than the normal control group.

Wagner, Roschke, Fell and Frank (1997) examined the P300 to all single trial responses (target and non-target) in groups with depression, schizophrenia and normal controls. Amplitude distributions of single trials' maximum positive deflections (P300) for both target and non-target stimuli were determined, and served as a basis for calculating the discrimination index  $d'$ . This index characterised differences in the electrophysiological responses to target and non-target stimuli and was significantly lower for patients with schizophrenia than for controls and depressive subjects. Thus, calculating  $d'$  on the basis of single trial analysis differentiated between schizophrenics and depressives, while there was no significant difference between the two groups on the traditionally averaged P300 component

elicited by target stimuli (Roschke & Fell, 1997; Wagner, Roschke, Fell, & Frank, 1997; Wagner, Roschke, Grozinger, & Mann, 2000). This suggests that it is not only necessary to examine the ERPs to target and non-target stimuli, but it is also necessary to investigate the relationship between target and non-target ERPs as this may be important to the specificity of ERP findings in schizophrenia. Studies 2 and 4, in the current thesis have investigated the contrast between ERPs elicited by target and non-target stimuli.

#### 2.4.6 Theoretical interpretations of the P300 deficit in schizophrenia

P300 amplitude has been envisaged as a general index of cognitive processing, however its specific meaning continues to be debated. The major theoretical interpretation of P300 amplitude is that it is generated by "tasks that are required in the maintenance of working memory" (Donchin, Karis, Bashore, Coles and Gratton, 1986, p 256). P300 has been demonstrated to follow the decision "target or non-target?" as subjects can accurately respond to target stimuli before the peak of the P300 component (Ritter, Simson, & Vaughn, 1972; Picton, Hillyard & Galambos, 1976). Verleger (1988) suggests that it represents perceptual closure, i.e. the P300 is evoked by 'awaited' stimuli when participants deal with repetitive highly structured tasks. On the other hand, Donchin and Coles (1988) suggest it may represent context updating when stimulus events require that an individual's model of the environment must be revised. This refers to the updating of memory after incoming information has been evaluated. In addition to stimulus probability, the extent to which this updating process is activated depends upon the value, significance or relevance of the stimulus (Sutton & Ruchkin, 1984). These authors

stress that this is a parietal P300 because of 'awaitedness', not 'unexpectedness', i.e. P300b reflects suspense and P300a a surprise. Both Verleger and Donchin agree that P300 is concerned with expectancy: for Donchin P300 reflects 'expectancy violation' whereas Verleger sees the P300 as the result of 'expectancy confirmation'.

However, there are criticisms of each of these hypotheses. A criticism of Donchin's hypothesis of memory updating is that the P300 occurs in situations in which one would not think that updating is necessary Picton (1992) suggests that in the usual oddball task the brain should quickly develop a memory model that incorporates the possibility of an occasional target stimulus. Updating this model should not be necessary each time the target occurs. The relationship of P300 to expectancy and probability has been challenged by the target to target interval (TTI) hypothesis (Gonsalvez et al., 1999; Gonsalvez & Polich, 2002; Croft, Gonsalvez, Gabriel & Barry, 2003). The TTI hypothesis proposes that increased P300 amplitude could be better explained by target to target interval (TTI) than by expectancy. The TTI hypothesis is reviewed in more detail in Chapter 6. Picton et al. (1992) hypothesised that P300 reflects the transfer of information from automatic to controlled processing or consciousness, yet P300 waves have been recorded in patients who are not conscious of the stimuli (Shefrin, Goodin, & Aminoff, 1988).

Another approach to understanding the meaning of P300 amplitude has been to correlate P300 amplitude with neuropsychological measurements. P300 amplitude reduction has been correlated with poorer performance on tests of memory (Neiman et al., 2002), including the verbal paired-association sub-test of the Weschler Memory Scale (Nagasawa et al., 1999), and lower IQ (Shajahan, O'Carroll, Glabus,

Ebmeier, & Blackwood, 1997). Prolonged P300 latency has been correlated with verbal fluency scores (Souza et al., 1995). P300 amplitude reduction was also correlated to measures of disability of daily life (Iwanama, Yamashina, Kazamatsuri, & Kamijima, 1999).

Intracranial recordings describe both P3a and P3b generators for the P300 elicited to target stimuli (Halgren, Marinkovic & Chauval, 1997). The P3a, related to the orientation of attention, is thought to occur in para-limbic and prefrontal networks (Halgren et al., 1997; Yamaguchi & Knight, 1991; Yamaguchi & Knight, 1993). The P3b, associated more with contextural integration, is generated in the temporo-frontal region (ventrally), association cortices (temporo-parietal region) and the hippocampus (Frodl-Bauch, Bottlender, & Hergerl, 1999 for review; Halgren, Squires, Wilson, Rohrbaugh, Babb & Crandall, 1980; Halgren, Marinkovic & Chauvel, 1997; Okada, Kaufman, & Williamson, 1983). Functional neuroimaging studies indicate that the P300 signal discrimination process engages preferential anterior and posterior cingulate, supramarginal gyrus (SMG) and hippocampal networks (Clark, Fannon, Lai & Benson, 2001; Kiehl, Laurens, Duty, Foster & Liddle, 2001; McCarthy, Luby, Gore & Goldman-Rakic, 1997).

Research findings on whether: the P300 is a state or trait deficit; ERP disturbances are present at onset of illness and/or different from chronic schizophrenia; and also the differential effects of non-target sequence effects, age and gender on ERPs in schizophrenia compared with normal controls; topography;

and symptom relationship to ERP deficits are discussed in Chapter 4, and provide the rationale for Study 2.

## 2.5 BEFORE THE P300: TARGET AND NON-TARGET N100 P200

### 2.5.1 Rationale for investigating ERPs to non-target stimuli

In auditory oddball studies, ERPs elicited by non-target stimuli are occasionally presented graphically, but are not usually the focus of investigation or analysis. However, recent research suggests that there are both theoretical and empirical indications for investigating possible ERP disturbances to non-target stimuli in addition to target stimuli in people with schizophrenia. Houghton and Tipper's (1996) model of "normal" selective attention proposes that, in addition to the excitatory feed back loop elicited by target stimuli, selective attention involves an inhibitory feedback loop elicited by non-target stimuli (see Figure 2.1). Thus ERP responses to non-target stimuli, would reflect how the brain, when involved in an oddball paradigm, processes information which is not task relevant.



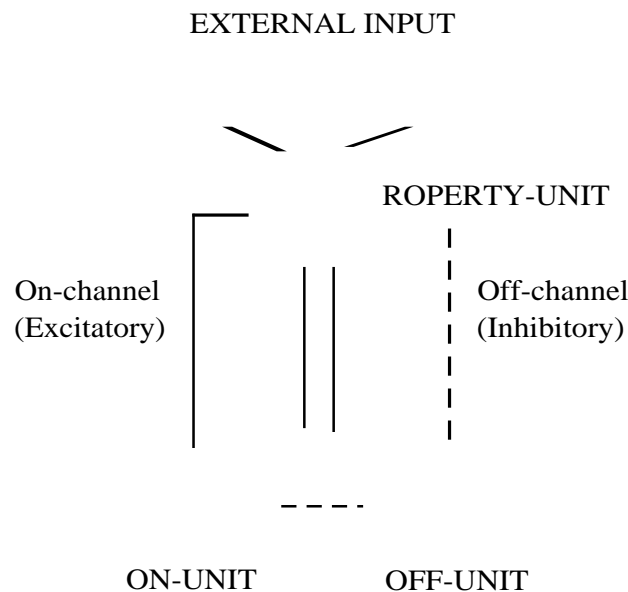


Figure 2.1 Model of the response system in selective attention (Houghton and Tipper, 1996, p27).

Evidence of cognitive effects on ERPs to non-targets has come from comparisons with ERPs elicited by 'neutral' stimuli, delivered while the subject is not involved in any related cognitive task (Desmedt & Tomberg, 1991). Garcia-Larrea, Lukaszewicz and Mauguire (1992) compared ERPs to non-target stimuli in an active oddball (count response required to target), a passive oddball (no instructions given to subjects), and a neutral, ignore condition (only non-target stimuli). ERPs elicited by non-target tones during either the passive or active oddball, showed consistent differences when compared to ERPs to the neutral condition, with N100 and P250 amplitudes enhanced in the two former conditions. Notably, the P250 component was not even present in 8 of the 10 subjects during the neutral runs. There were early and late effects associated with N100 amplitude to

non-target stimuli. The early effect found in all three conditions was maximal centrally and disappeared with progression of the experiment. This effect was interpreted to reflect changes in a vigilance-related component, the disappearance seen as progressive optimisation of the alerting state. The later effect was not found in the neutral condition and was more important in the active than passive oddball. It was predominantly frontal, with higher amplitude over the right hemisphere and persisted to the end of the recording session. This effect was thought to be *processing negativity* evoked by active discrimination from relevant target tones. Similarly Yordanova, Kolev and Polich (2001) found event-related desynchronisation in the alpha band to stimuli when used as non-targets in the auditory oddball but no alpha event related desynchronisation when the same stimuli were used for passive listening.

#### 2.5.2 Rationale for examining N100 and P200 components to target and non-target stimuli and their differentiation

As participants can accurately respond to target stimuli before the peak of the P300 component (Ritter, Simson, & Vaughn, 1972; Picton, 1992) the decision "target or non-target?" may have preceded the process that generates the P300. Goodin, Aminoff, and Mantle (1986) suggest that the decision also precedes the N200 component, based on changes in the EMG prior to the response. Models which propose a deficit at the comparator stage (Gray, 1998; Hemsley, 1996) and stress a failure in the inhibitory effect of context (Servan-Schreiber, et al., 1996) would thus predict an earlier disturbance that perhaps might be reflected in deficits of N100 and P200, elicited by both target and non-target stimuli in addition to the P300 deficit.

Consistent with some current theories (e.g. Gray, 1998; Hemsley, 1996), critical dysfunctions in schizophrenia could relate to mechanisms that are called into play when switches from one stimulus to another occur. Such processes may be best captured by differential response to target and non-target stimuli rather than by studying only target related ERPs. In support of this, in a single trial study of P300 (Wagner et al., 1997) it was the discrimination index  $d'$  that was specific to schizophrenia compared to depression (see 2.3.5). There is also evidence that N100 and P200 components elicited by target and non-target stimuli are sensitive to schizophrenia. Boutros et al. (1997) suggest from their data that N100 and P200 elicited by target and non-target stimuli are helpful in diagnostic classification, and Ford, Mathalon, Kalba, Marsh and Pfefferbaum (2001) demonstrated that N100 amplitude reduction to targets and non-targets is more specific to the "core pathophysiology" of schizophrenia than P300 reduction and "deserves more study" (p857). The current thesis provides a detailed examination of N100 amplitude to target and non-target stimuli.

There are additional indications of disturbances in earlier components which might have later 'flow on' effects on the P300 from studies which have found reduced P50 suppression (Yee, Nuechterlein, Morris, & White, 1998) and mismatch negativity (MN/IN) in schizophrenia (Javitt, Doneshka, Grochowski, & Ritter, 1995; Mitchie et al., 2000; Shelley et al., 1991). MMN is a negative component of the ERP elicited by a discriminable change in a repetitive background of auditory stimulation, while the subjects attention is directed elsewhere, eg reading a book (Michie, 2001). Unlike components elicited to the auditory oddball in this thesis, in which a response is required to the deviant (target) stimuli, the MMN does not rely on attention to, or

detection of the deviant stimuli. Javitt et al. (1993) suggests MMN reflects widespread dysfunction of working memory. However, Michie (2001) suggests that it represents an abnormality within the window of temporal integration, that is coincident with the early phase of auditory sensory memory. As this thesis focuses on the oddball paradigm an in depth review of the MMN is beyond the scope of the thesis (for a review of this literature see Michie, 2001).

### 2.5.3 N100 component

N100 is involved in stimulus classification: the decision to further process information or ignore them (Fabiani, Gratton, & Coles, 2001; Kok, 1997). Several studies have demonstrated correlations between N100 and specific aspects of stimulus features (Naitanen & Picton, 1987; Pritchard, 1986), and between N100 and attention, with N100 amplitude larger with increases in attentional requirements (Maclean, Ohman, & Lader, 1975; Pritchard, 1981) whether automatic or directed (Ford, Roth, Menon, & Pfefferbaum, 1999). N100 amplitude is also related to arousal and is enhanced with caffeine (Bruce, Scott, Shine, & Lader, 1992) and diminished with alcohol (Pfefferbaum, Roth, Tinkleberg, Rosenbloom, & Kopell, 1979). Ford et al. (1994), found that during antipsychotic treatment larger N100 amplitude to target and non-target stimuli were associated with higher levels of methoxyhydroxyphenylglycol which they interpreted to suggest an influence of arousal.

N100 amplitude shows a systematic reduction in amplitude when the eliciting stimulus is repeated (for both attend and ignore instructions) usually in habituation paradigms. Whether this reflects a cognitively relevant process, or a more basic neurophysiological process is not clear, i.e. can it be seen as habituation, as defined by orienting response theory (Sokolov, 1963), or a process involving the recovery cycle or refractory period of the neural generators underlying the N100 (Callaway, 1973; Naatanen and Picton, 1987). This attenuation has often been reported as habituation. However, some studies (Barry, Cocker, Anderson, Gordon, & Rennie, 1992; Budd, Barry, Gordon, Rennie, & Mitchie, 1998) have challenged this, as there is no evidence of dishabituation following the change stimulus. These studies suggest support for the view that the N100 decrement is due to refractory periods or recovery cycle processes of at least two generators contributing to activity in the N100 peak latency range. Recovery cycle or refractory cycle effects reflect the dissipation of a state of temporal excitability of the N1 generators following their activation by a stimulus (Callaway, 1973; Wastell, 1980). It is generally maintained that closely spaced presentations of auditory stimuli do not allow adequate recovery of these mechanisms and produce a decline in N1 amplitude (Callaway, 1973; Naatanen and Picton, 1987). However in direct contrast to this, N100 amplitudes to frequent tones (non-targets) in the oddball paradigm have been found to change across the stimulus sequence, with larger amplitudes associated with longer trains of frequent stimuli (Hermanutz, Chen, & Sommer, 1981; Hirata & Lehman, 1990; Starr, Aguinaldo, Roe, & Michalewski, 1997). This increase in N100 to non-target stimuli with stimulus repetition challenges a recovery cycle explanation.

Genetic analysis of ERPs suggests that several regions of the human genome contain genetic loci related to the generation of N100, in particular the GABA (A) receptor (Porjesz et al., 2002; Uraski, Ogura, Hirano, & Tomori, 1994). Additionally, increased levels of GABA may affect N100 by reducing the signal that is recorded over the prefrontal area of the brain (Winterer et al., 2000)

#### 2.5.4 N100 in schizophrenia

##### Target stimuli

Reduced N100 amplitude to target stimuli has been found in both medicated and unmedicated patients with schizophrenia (Blackwood et al., 1987; Ford et al., 1994; Ford et al., 1999; Ogura et al., 1991; Pfefferbaum, Wenegrat, Ford, Roth, & Kopell, 1984; Pfefferbaum, Ford, White, & Roth, 1989; Pritchard, 1986; Roth, Horvath, Pfefferbaum, & Kopell, 1980; Roth, Pfefferbaum, Kelly, Berger, & Kopell, 1981; Roth Goodale, & Pfefferbaum, 1991; Shagrass, Straumanis, Roemer, & Armadeo, 1977; Shagrass, Roemer, Straumanis, & Armadeo, 1978). It is thus unlikely to be solely related to drug effects, despite reports that neuroleptic medication reduces N100 amplitude (Baribeau-Braun, Picton, & Gosselin, 1983; Pfefferbaum, Ford, White, & Roth, 1989). N100 latency to target stimuli has either been found not to differ (Ford et al., 1994; Boutros et al., 1997; Laurent et al., 1998) or to be earlier (Ford et al., 2001) for schizophrenia compared to controls.

##### Non-target stimuli

Reduced N100 amplitude to non—target stimuli has also been found in both medicated (Pfefferbaum et al., 1984; Roth & Cannon, 1972) and unmedicated (Laurent et al., 1999) patients with schizophrenia. Roth and Cannon (1972) further

clarified that N100 amplitude was larger for controls only for either target stimuli or non-target stimuli that immediately precede a target, but not for the first or second non-target that followed a target stimulus. However this study employed an ignore condition, with no response required to target stimuli. Studies 2 and 4 (Chapters 5 & 7) in the current thesis examine these effects in the more commonly used attend paradigm in which the subject is asked to respond to target stimuli.

Ford et al. (1994) found delayed N100 latency to non-targets. Other studies have not found significant differences in N100 latency to non-target stimuli in schizophrenia (Boutros et al., 1997, Laurent et al., 1999).

#### 2.5.5 P200 component

The P200 component may represent inhibition of sensory input from further processing (Hegerl & Juckel, 1993; Schupp, Lutzenberger, Rau, & Birbaumer, 1994) and is normally associated with automatic stimulus identification and discrimination (Lindholm & Koriath, 1985). Although the topography of N100 amplitude to target and non-target stimuli is similar, there are differences in topography between target and non-target P200 amplitude. This difference appears to result from the distortion introduced by the concurrent negative shift of the N200 (Simson, Vaughan, & Ritter, 1977). Topographically, P200 to non-target stimuli is maximal centrally (Amenedo & Diaz, 1998).

### 2.5.6 P200 component in schizophrenia

The P200 has been reported to be earlier, or larger in people with schizophrenia (Pfefferbaum, Horvath, Roth, Tinklenberg, & Kopell, 1980; Roth, Horvath, Pfefferbaum, & Kopell, 1980), decreased in some studies (Faux et al., 1987), but not different in other studies (Ford et al., 1994). No difference in P200 amplitude and latency to non-target stimuli was found in studies with unmedicated patients (Ford et al., 1994; Laurent et al., 1999). However, Ogura et al. (1991) found P200 amplitude increased in patients withdrawn from medication.

## 2.6 CONCLUSION

Most oddball research in schizophrenia has focused on the P300 component, however both the theoretical and empirical evidence reviewed in this Chapter indicate the need to investigate ERPs to non-targets in addition to targets in schizophrenia. This evidence emphasizes the necessity for examination of the differences between N100 and P200 components elicited by target and non-target stimuli in schizophrenia as compared to normal controls.



### 3 STUDY 1: ERP COMPONENTS ELICITED BY TARGET AND NON-TARGET STIMULI IN SCHIZOPHRENIA AND NORMAL CONTROLS.

The main results of this study have been published (Brown et al., 2000, see Appendix 2 for a copy of the article). A more complete account of the Study and its results is presented below.

#### 3.1 INTRODUCTION

The review of the oddball ERP literature in schizophrenia in Chapter 2 indicated a focus on the robust P300 deficit. However the usefulness of this finding as a biological marker for schizophrenia is limited by its lack of specificity. Theoretical and empirical findings (see Chapter 2, 2.5.1 and 2.5.2) provide some support for the notion that a comparator disturbance in schizophrenia, leading to a failure to make use of context in information processing, might occur 100-200ms post-stimulus and consequently would be better captured in the differentiation between target and non-target ERP components, particularly the earlier N100 and P200 components. ERP studies in schizophrenia have focused mainly on the P300 component elicited by target stimuli, many restricting their analysis solely to P300. Less attention has been given to earlier N100, P200 components to target stimuli and even less to non-target stimuli (see Chapter 2, 2.5.4 and 2.5.6). This study investigated deficits in earlier components, N100 and P200, to both target and non-target stimuli in schizophrenia, in addition to the later components N200 and P300.

#### 3.2 HYPOTHESES

a) Between groups, Non-targets

1. The N100 to non-target stimuli will be reduced and occur later in the schizophrenia group.

2. P200 amplitude will be reduced or not differ and P200 latency will be earlier, to non-target stimuli in the schizophrenia group.

b) Between Groups, Targets

1. N100 will be reduced and earlier to target stimuli in the schizophrenia group.
2. P200 will be increased and delayed to target stimuli in the schizophrenia group.
3. N200 will be reduced and delayed to target stimuli in the schizophrenia group.
4. P300 will be decreased and delayed to target stimuli in the schizophrenia group.

c) Group by Stimulus Contrasts

1. N100 will be increased and delayed to target compared with non-target stimulus in the control but not the schizophrenia group.
2. P200 amplitude will be increased and prolonged to non-target compared with target stimulus in the control but not the schizophrenia group.

### 3.3 METHOD

#### 3.3.1 Participants

Forty participants with Schizophrenia (11 females and 29 males; mean age 35.45 years, range 20 to 53 years) were recruited from hospitals and community

centres in Sydney. Each participant was interviewed with Sections G (Schizophrenia and other psychotic disorders), M (Organic mental disorders), and P (interviewer observations) from the Composite International Diagnostic Interview (CIDI) (World Health Organisation, 1992a), resulting in a DSM-IV (American Psychiatric Association, 1994) and ICD10 (World Health Organisation, 1992b) diagnosis of schizophrenia. Exclusion criteria for both this group and for the normal control group were a recent history of substance abuse, epilepsy or other neurological disorders, and mental retardation or head injury, assessed using section M from the Composite International Diagnostic Interview (World Health Organisation, 1992a) and the Westmead Hospital Clinical Information Base questionnaire. After interview, schizophrenic symptoms were rated by the participating psychiatrist, using the Positive and Negative Syndrome Scale (PANNS) (Kay and Opler, 1987). The mean chlorpromazine equivalent for medication in the participants with schizophrenia was  $660.5 \pm 636.6$  mg.

Forty control participants (mean age 36.7 years, range 20 to 54 years) were drawn from the general population and were age and gender matched to within 5 years with the schizophrenia group. Control participants were screened for history of psychiatric illness (themselves or first degree relative). The Westmead Hospital Clinical Information Base questionnaire was also used to obtain demographic information for both groups.

### 3.3.2 Data Acquisition Procedure

All participants were asked to refrain from drinking caffeine or smoking for at least three hours prior to their recording. Participants were seated in a reclining

chair in a quiet, dimly lit laboratory; facing a video screen and wearing a pair of headphones (see Figure 3.1). To reduce eye blinks, participants were instructed to look at a small dot on a computer screen placed 60 cm in front of them during the task. The Study was approved by Western Area Health Service and University of Wollongong ethics' committees.

A conventional auditory oddball paradigm was employed, consisting of 40 target tones (1500 Hz with 15% probability and 247 non-target (1000 Hz) tones both lasting 50ms (with 10ms rise and fall). The tone intensity was 60 dB SPL and the interstimulus interval (IR) was 1.3 s. Participants were asked to ignore the low pitched (non-target) tones and press two reaction time buttons (with the index finger of each hand, to control for possible lateralised effects of motor responding) when they identified a high pitched (target) tone. Speed and accuracy of response were emphasised equally. EEGs were recorded on a DC based system (Synamps equipped with a 16-bit AID converter) from 19 scalp sites (Fp 1, Fp2, Fz, F3, F4, F7, F8, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, O2) according to the 10-20 International system (Bloom, 1982) in reference to linked-ear electrodes. In this Study analysis was restricted to midline sites, while full topography is analysed in Study 2. The sampling rate was 250 Hz. A low pass filter was applied to the signals prior to digitization. The cut-off of this filter was 50 Hz, with attenuation being 40dB/decade above 50 Hz. In addition, a 50Hz notch filter was applied to eliminate 50Hz AC mains power supply interference. Horizontal eye movement potentials were recorded using two electrodes, placed 1 cm lateral to the outer canthus of each eye. Vertical eye movement potentials were recorded using two electrodes, placed on the middle

of the supraorbital and infraorbital regions of the left eye. Impedance for all electrodes was less than 5 kOhms.

EOG correction was carried out off line using a standard procedure (Gratton, Coles, & Donchin, 1983). Only correctly identified target epochs for which a button press response was obtained within one second of the target tone were analysed. Averaged ERPs to target stimuli were computed and N100, P200, N200 and P300 peaks were measured relative to a prestimulus (200ms) baseline by an automated system based on the detection of a consistent change in the sign of the gradient of the wave form. Thus a change from a consistently positive to a consistently negative gradient was identified as a positive peak, and vice versa for a negative peak (Haig, Gordon, Rogers, & Anderson, 1995) with the criteria that N100 occurred between 80-140ms, P200 between 150-240ms, N200 between 200-280ms and P300 between 250-500 ms. Peaks thus identified were then verified through visual inspection. N100 and P200 peaks in averaged ERPs to non-targets before and after were ascertained according to the same method.

Figure 3.1 Picture of a participant, fitted with the electrocap, in the laboratory.

### 3.3.3 Analysis

N100 and P200 amplitudes and latencies were submitted separately to a 3 way ANOVA repeated measures design, incorporating group (schizophrenia vs. controls) by stimuli (target vs. non-target) by electrode site (Fz, Cz, Pz), with repeated measures for stimulus and site factors. For the site factor, linear and quadratic contrasts were examined, the linear contrast purporting to examine reduced amplitudes at parietal sites (Fz vs. Pz) and the quadratic contrast purporting to test the frequently observed maximal amplitudes at central sites (Cz vs. Fz + Pz). N200 and P300 components were reliably observed only to the target stimulus and were, therefore, subjected to a two way ANOVA, incorporating group (schizophrenia vs. controls) and electrode site (Fz, Cz, Pz) with repeated measures for the site factor. Similar linear and quadratic contrasts as above were carried out for the site factor. Only results from midline sites are included in this Study, full topography is examined in the second Study (Chapter 5).

## 3.4 RESULTS

Average ERPs for midline sites are presented in Figure 3.2 (between-groups) and Figure 3.3 (within group). Means and standard deviations for each component amplitude and latency appear in Table 3.1. A small percentage (between 1% and 2.5% in each group) of ERP measures were identified as outliers (greater or less than one and a half the interquartile range from the upper and lower quartile). Because

results remained unchanged following removal of outliers only results based on entire dataset (with outliers) is presented here.

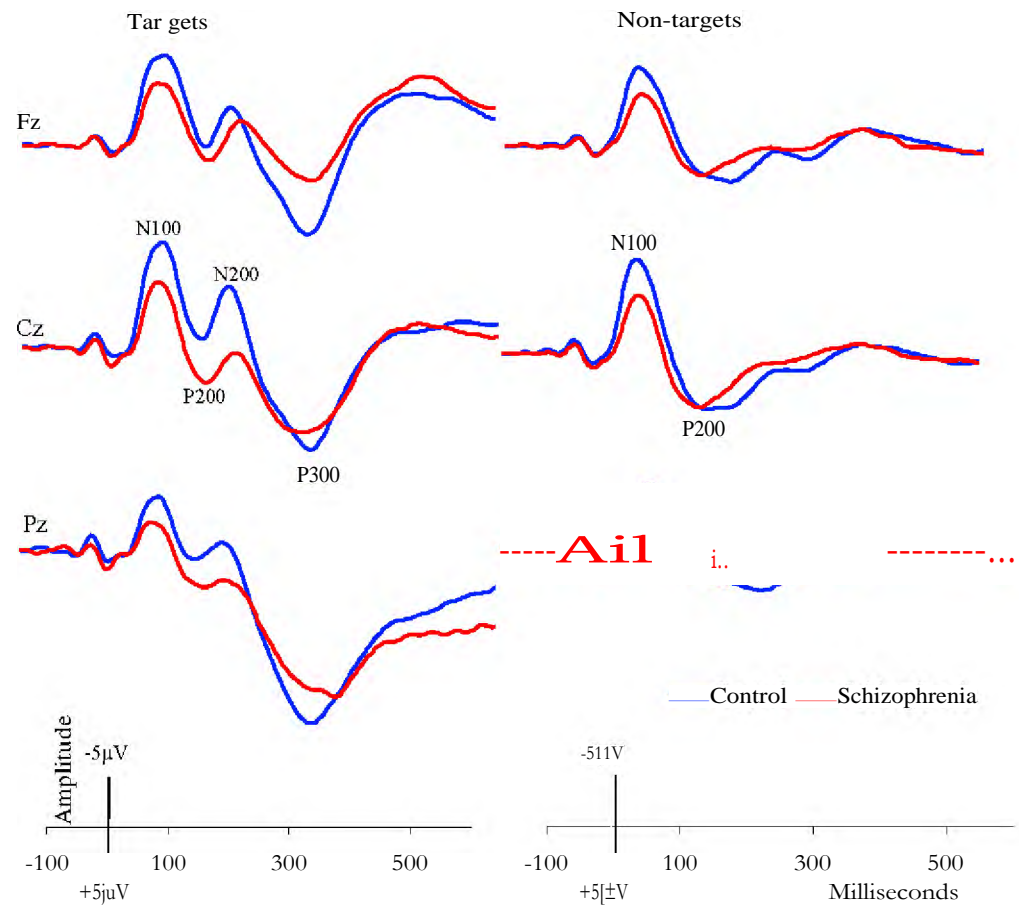


Figure 3.2 Between-Group ERP differences for target and non-target stimuli.

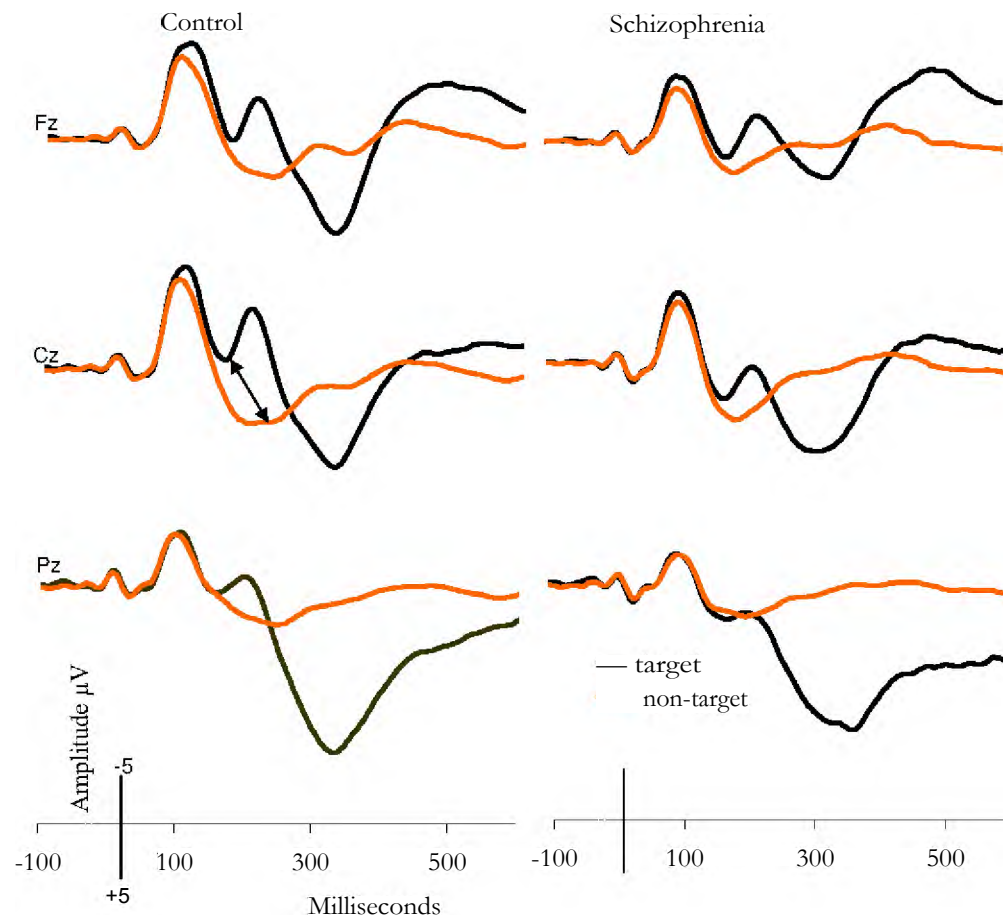


Figure 3.3 Within-group ERP differences for target and non-target stimuli.



Table 3.1 Component means and standard deviations (SD) for control and schizophrenia groups to target and non-target stimuli.

		Target				Non-target			
		Control		Schizophrenia		Control		Schizophrenia	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
N100 amplitude	Fz	-10.01	3.06	-7.11	3.10	-7.99	2.80	-5.35	2.65
	Cz	-11.57	3.68	-7.34	3.36	-9.42	3.41	-5.88	2.61
	Pz	-6.48	2.73	-3.74	2.44	-5.41	2.45	-3.33	1.45
N100 latency	Fz	108.60	13.61	102.70	17.60	100.60	13.24	103.28	13.73
	Cz	105.80	10.55	98.78	11.28	99.00	9.26	99.25	8.03
	Pz	103.30	10.57	94.55	13.36	99.40	8.09	99.00	13.01
P200 amplitude	Fz	1.17	4.27	2.86	4.61	3.97	3.00	3.33	2.73
	Cz	0.10	4.28	5.41	5.35	6.45	3.70	5.59	2.74
	Pz	1.93	3.79	4.61	4.03	3.70	3.09	3.40	2.10
P200 latency	Fz	171.14	16.19	173.35	19.05	204.50	31.02	184.20	24.13
	Cz	164.42	15.11	173.88	21.64	209.03	31.27	182.65	21.56
	Pz	161.26	20.38	169.22	33.29	198.63	39.72	179.00	27.82
N200 amplitude	Fz	-5.28	3.72	-5.08	4.94				
	Cz	-7.62	6.52	-2.40	6.46				
	Pz	-2.62	5.24	0.20	5.76				
N200 latency	Fz	215.85	19.12	227.93	35.50				
	Cz	210.15	19.29	226.15	40.55				
	Pz	202.57	22.50	223.39	40.47				
P300 amplitude	Fz	9.92	6.45	5.00	5.79				
	Cz	11.18	8.15	10.35	7.13				
	Pz	17.38	7.59	15.01	7.14				
P300 latency	Fz	323.33	25.20	327.28	34.23				
	Cz	322.69	29.21	327.98	49.64				
	Pz	334.83	37.50	350.38	48.03				

### 3.4.1 N100

#### Amplitude

Main effects were significant for group,  $F(1,78) = 30.8$ ,  $p < .001$ , with the schizophrenia group showing reduced N100 amplitude compared with controls, and for stimulus,  $F(1,78) = 58$ ,  $p < .001$ , with N100 amplitude for non-target stimuli reduced compared to target stimuli. Significant linear,  $F(1,78) = 130.56$ ,  $p < .001$  and quadratic,  $F(1,78) = 259.51$ ,  $p < .001$  contrasts for the site factor indicated N100 amplitude was maximal fronto-centrally. The main effect for group was qualified by a significant quadratic contrast for Group X Site,  $F(1,78) = 5.97$ ,  $p < .01$ , as the between-group difference was maximal at the vertex compared with frontal and parietal sites. Significant linear  $F(1,78) = 21.45$ ,  $p < .001$  and quadratic  $F(1,78) = 25.02$ ,  $p < .001$  contrasts, for Stimulus X Site arose as the reduction to non-target compared with target N100 amplitude was maximal at fronto-central sites.

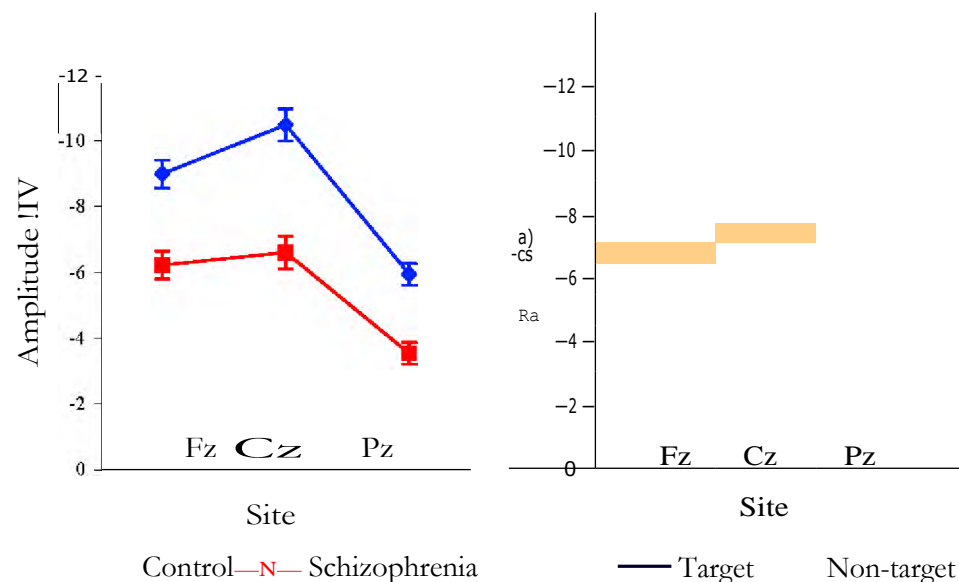


Figure 3.4 N100 amplitude for control and schizophrenia groups, across stimuli, at midline sites (left). N100 amplitude to target and non-target stimuli, across group, at midline sites

### Latency

The main effect for group was not significant,  $F(1,78) = 2.9$ ,  $p = .09$ , however there was a Stimuli X Group interaction,  $F(1,78) = 9.8$ ,  $p < .01$ , as N100 latency was significantly delayed for target compared to non-target stimuli for the control but not the schizophrenia group (see Figure 3.4). There was a significant linear contrast for site,  $F(1,78) = 16.20$ ,  $p < .001$ , with N100 latency prolonged at Fz.

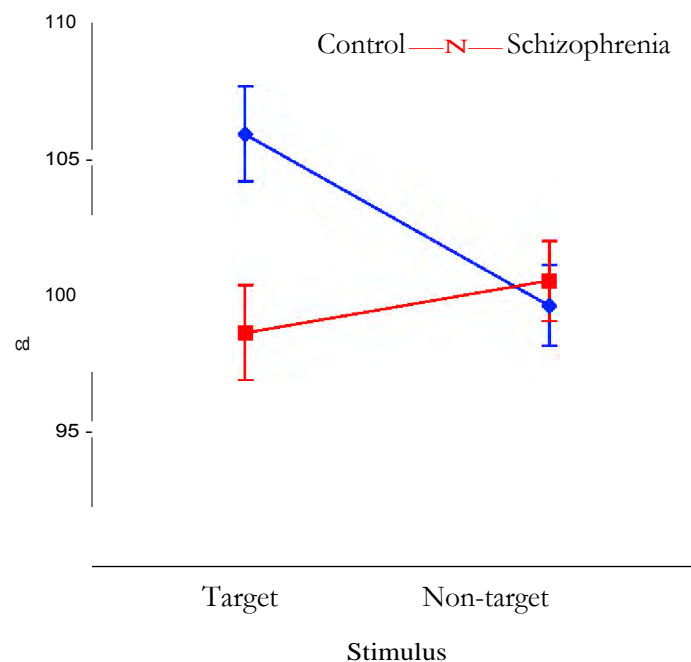


Figure 3.5 N100 latency to target and non-target stimuli, across sites.

### 3.4.2 P200

#### Amplitude

Main effects were significant for group,  $F(1,78) = 5.3$ ,  $p < .05$ , with the schizophrenia group showing increased P200 amplitude overall, and for stimulus,  $F(1,78) = 16.3$ ,  $p < .001$ , with P200 reduced to target compared with non-target

stimuli. There was a quadratic contrast for site, with P200 maximal at Cz compared with Fz and Pz. These main effects were further qualified by a significant Group X Stimulus,  $F(1,78) = 19.8$ ,  $p < .001$ , Group X Site (quadratic contrast),  $F(1,78) = 10.0$ ,  $p < .01$  and Group X Stimulus X Site (quadratic contrast),  $F(1,78) = 22.69$ ,  $p < .001$ , interactions. Whereas the schizophrenia group responded similarly to target and non-target stimuli, normal controls responded differentially with decreased P200 to target compared with non-target stimuli, with this difference most marked at Cz (see Figure 3.6).

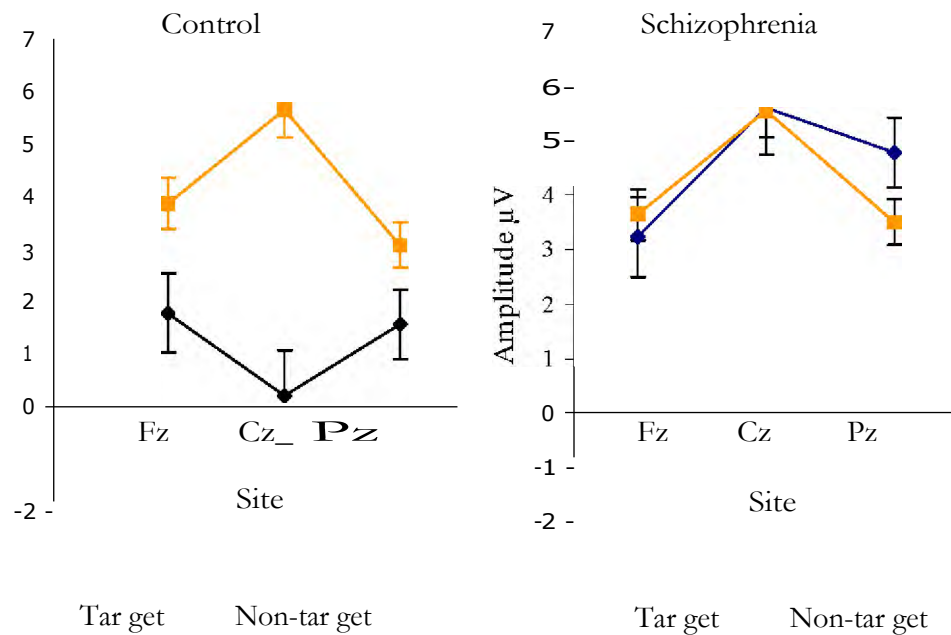


Figure 3.6 P200 amplitude to target and non-target stimuli.

## Latency

Main effects were significant for group,  $F(1,78) = 5.2$ ,  $p < .05$  with the schizophrenia group demonstrating earlier P200 latency overall; for stimulus,  $F(1,78) = 53.2$ ,  $p < .001$ , with a delay to non-target stimuli compared with target stimuli; and for site with a significant linear contrast,  $F(1,78) = 6.34$ ,  $p < .05$ , which was maximal fronto-centrally. The Group X Stimuli interaction,  $F(1,78) = 18.77$ ,  $p < .001$ , for P200 latency, arose because there was a pattern of prolonged P200 latency for non-target compared with target stimuli for the control but not the schizophrenia group, which resulted in an earlier P200 latency to the non-target stimulus for the schizophrenia compared with controls (see Figure 3.7).

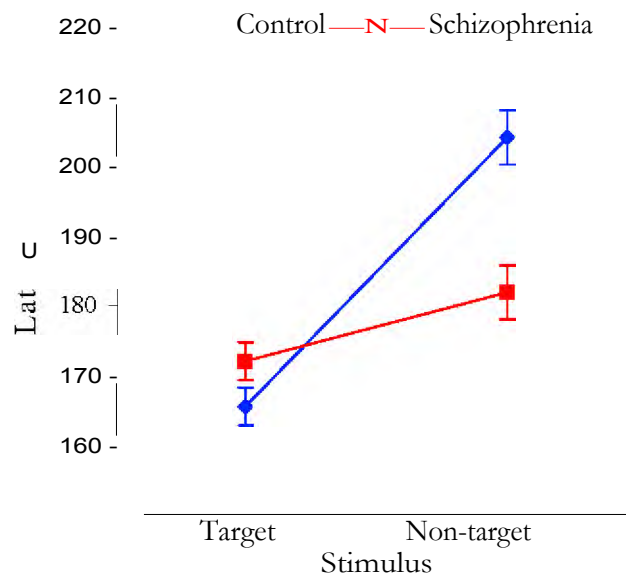


Figure 3.7 P200 latency to target and non-target stimuli.

### 3.4.3 N200

#### Amplitude

The main effect for group was significant,  $F(1,78) = 6.9$ ,  $p = .01$ , with N200 amplitude reduced for the schizophrenia group. Significant linear,  $F(1,78) = 39.5$ ,  $p < .001$ , and quadratic,  $F(1,78) = 18.12$ ,  $p < .001$ , contrasts for site, indicated a fronto-central maximum for N200 amplitude. These main effects were further qualified by significant Group X Site linear,  $F(1,78) = 4.29$ ,  $p < .05$ , and quadratic  $F(1,78) = 18.97$ ,  $p < .001$ , contrasts. In sum, as compared with the normal controls, the schizophrenia group produced reduced N200 amplitudes, with this reduction being specific to central and parietal sites.

#### Latency

The main effect for group was significant,  $F(1,78) = 7.2$ ,  $p < .01$ , for N200 latency, with the schizophrenia group delayed overall. A significant linear contrast for site,  $F(1,78) = 7.55$ ,  $p < .01$ , indicated that N200 latency was prolonged at Fz compared with Pz for all subjects.

### 3.4.4 P300

#### Amplitude

The main effect for group was significant,  $F(1,77) = 4.4$ ,  $p < .05$ , with P300 amplitude reduced overall in the schizophrenia group. There were also significant linear,  $F(1,77) = 119.4$ ,  $p < .001$ , and quadratic,  $F(1,77) = 7.87$ ,  $p < .01$ , contrasts for site, with P300 amplitude maximal at centro-parietal sites for all subjects. These main effects were further qualified by a Group X Site quadratic contrast,  $F(1,77) =$

13.03,  $p < .001$ , as the reduction in P300 amplitude for the schizophrenia group was maximal frontally and parietally compared with the vertex (See Figure 3.8).

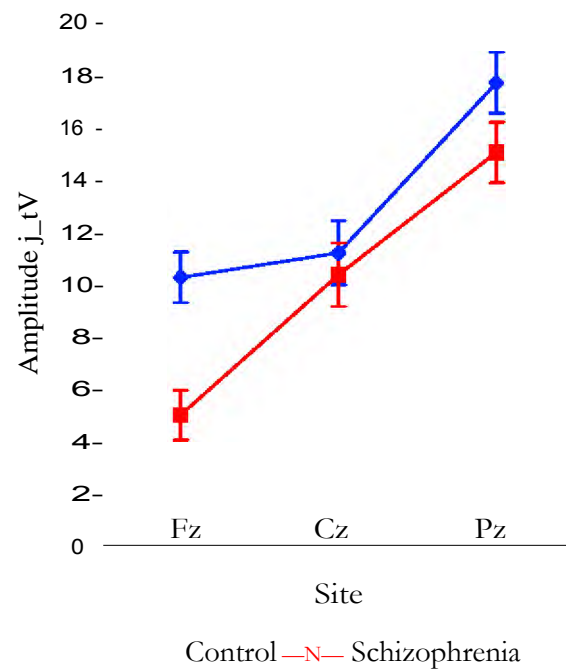


Figure 3.8 P300 amplitude for schizophrenia and control groups at midline sites.

#### Latency

Effects were not significant for group. For site, there were significant linear,  $F(1,77) = 11.68$ ,  $p < .001$ , and quadratic,  $F(1,77) = 5.68$ ,  $p < .05$ , contrasts demonstrating prolonged latencies at parietal compared with fronto-central sites for both groups.

### 3.4.5 Response Time

The schizophrenia group had a mean RT of 384ms (SD = 90ms) which was significantly slower,  $t(1,76) = -4.43$ ,  $p < .001$ , than the control group, with a mean RT of 309ms (SD = 50ms).

## 3.5 DISCUSSION

Few studies have examined ERPs to non-target stimuli or systematically focused on components prior to the P300 complex. This Study was primarily designed to examine differences in ERP components to target and non-target stimuli in patients with schizophrenia and age and sex matched controls. The results indicate significant group differences in early components to target and non-target stimuli validating this approach. Earlier components may not be as conspicuous as the larger P300, nevertheless reliable differences between groups emerged. The Study of ERPs elicited by target and non-target stimuli together has an additional advantage, as relational and interactive mechanisms between the two categories of stimulus can be examined. As hypothesised, the schizophrenia group responded similarly to the two stimuli, in comparison to the normal controls, who differentiated between the two stimuli on the N100 and P200 components.

The N100 amplitude deficit to non-target stimuli, across midline sites, in the schizophrenia compared to the control group, is consistent with previous studies with attend (Pfefferbaum, 1984; Laurant et al., 1999) and ignore (Roth & Cannon, 1972) instructions. The schizophrenia group also demonstrated earlier P200 latency to non-target stimuli, across midline sites, compared to controls as hypothesised. The



hypothesised decrease in P200 amplitude to non-target stimuli in the schizophrenia compared with control group was not found.

Consistent with previous literature (see Chapter 2), that focused on processing task relevant target stimuli, the patient group showed a decreased and earlier N100 amplitude (associated with attention) to target stimuli across midline sites, increased P200 amplitude to target stimuli maximal at the vertex, (associated with decision making), reduced and delayed N200 latency centro-parietally (associated with response selection) and diminished P300 amplitude frontally and parietally (associated with the context of information processing) which was also delayed parietally. The relational and interactive mechanisms between target and non-target stimuli are best reflected in the group by stimulus analyses. With the exception of N100 amplitude, the schizophrenia group did not differ in the way they responded to target and non-target stimuli. The normal controls, however, did differentiate, with delayed N100 latency and an earlier and reduced P200 to target compared to non-target stimuli. In the schizophrenia group N100 latency and P200 amplitude and latency to both target and non-target stimuli resembled the control group's response to non-target stimuli. The hypothesised group difference for within group N100 amplitude effects was not found as both groups showed reduced N100 amplitude to non-target compared to target stimuli.

The pattern of ERP response in the patient group therefore, was firstly diminished N100 to both non-target and target stimuli, reflecting globally diminished aspects of attention. Secondly, the earlier P200 response to non-target stimuli in patients, was enhanced in amplitude and delayed when processing target stimuli.

This may suggest that for nontarget stimuli there was a premature closure of decision making (reflected in earlier P200 latency), whereas for target stimuli there was an increased network activation (reflected in increased amplitude) and a consequent delayed speed of processing (reflected in P200 latency) in the patient group. However, it is difficult to disentangle target P200 amplitude and latency differences from the influence of the overlapping N200 component, and it is possible that these between-group P200 changes are influenced by differential N200 responses to the target stimuli.

This disturbance in the processing of target and non-target information is consistent with single trial P300 findings (Ford et al. 1994; Roschke et al., 1996), and with the Gray-Hemsley model, in which misattributions in the "match:mismatching" are proposed to underlie the positive symptoms in schizophrenia. Precisely how this misattribution effects subsequent information processing is not known. However, it may modulate the delay in N200 latency, and the decrease in processing the context of target information (as reflected in this Study and numerous other studies by decreased P300 amplitude). This would be consistent with Broadbent's (1958) suggestion that early stages of processing may lead to later dysfunctions.

This potential disturbance in selective processing of relatively relevant and irrelevant information is also consistent with an entirely different body of research. Positron emission tomography (PET) studies suggest that the anatomical circuitry involved in extracting relevant and filtering irrelevant information, particularly involves the pulvinar nucleus of the thalamus (Posner and Dehaene, 1994), and there

is some evidence that these circuits may be impaired in schizophrenia (Andreasen et al., 1994). These networks overlap with those suggested by Gray (1998), where familiar non-targets (match) and novel targets (mismatch) engage the reticular nucleus of the thalamus, but, thereafter, familiar stimuli activate ongoing processes in the basal ganglia, whereas novel stimuli activate the cingulate and exploratory processing networks.

These psychophysiological findings may also be linked to disturbances in neurochemistry. For example, there is a body of evidence linking dopamine hyperactivity to schizophrenia (Gray, 1991). Dopamine is thought to suppress spontaneous neural firing while enhancing the capacity of neural systems to increase activity in response to a specific stimulus or task (Foote and Morrison, 1986; Cohen and Servan-Schreiber, 1993). In addition, dextroamphetamine (indirect monoamine agonist) has been found to 'focus' neural activity that is specific for a particular task (Mattay et al. 1996).

However, these results are preliminary and raise several issues which need to be clarified. Firstly, this Study averaged all non-target stimuli together, however, there is evidence that non-target stimuli immediately before the target stimuli (T-1), and non-target stimuli immediately following the target stimuli (T+1), are processed differently (Hirata & Lehman, 1990) and that this process may be disturbed in schizophrenia (Roth and Cannon, 1972). It would be important to investigate these results with non-target stimuli subaveraged for T-1 and T+1 stimulus, as differences between N100 amplitude to target and non-target stimuli may have been obscured by averaging in this Study. Computing averaged ERPs to non-target and target stimuli

regardless of their sequential position (e.g. number of preceding target or non-target stimuli) obscures systematic ERP effects that may be observed when sequences are sorted and averaged separately (e.g., non-target following a target stimuli versus non-target preceding a target stimuli) according to their sequential position Secondly, the duration of illness ranging from 1 to 33 years, for patients in this Study, may have obscured changes in deficits with age and chronicity. It would be important to establish that these deficits are present at onset of illness, and are not a product of chronicity. Several other factors which could interact with these results and would also be important to investigate are the interaction of ERP results with symptom factors, the differential effects of aging and gender on ERPs in schizophrenia and normal controls, and an extension of analysis from midline sites to full topography. The sensitivity and specificity to schizophrenia of N100 and P200 to target and non-target stimuli in comparison with P300 amplitude also need to be demonstrated. These issues are explored in the following Chapters. Chapter 4 evaluates the existing literature and Study 2 (Chapter 5) is an empirical investigation (with the exception of specificity which is explored in Study 4 [Chapter 7]) of these issues.

## 4 BACKGROUND AND RATIONALE TO STUDY 2

### 4.1 ERPs AT FIRST ONSET OF ILLNESS VERSUS CHRONIC SCHIZOPHRENIA

Although numerous studies have found deficits in the ERPs of patients with schizophrenia to target stimuli, and in a smaller number of studies to non-target stimuli (reviewed in Chapter 2), most of these studies investigated ERPs in chronic patients. An important emerging issue is whether these deficits are trait-like, and therefore present at the onset and throughout the developmental course of illness, or whether they are markers of chronicity (Salisbury et al., 1998; Ford, 1999; Frodl-Bauch, Meisenzahl, Galinat, Hegerl, & Moller, 1998; Mathalon, Ford, & Pfefferbaum, 2000; Blackwood, 2000). This is significant because ERP deficits observed in patients with chronic schizophrenia may be secondary to chronic morbidity, neuroleptic medication, or other effects associated with chronic mental illness such as hospitalisation. If established as a trait, ERP deficits would be most useful in identifying "at risk" individuals, in addition to providing potential for the implementation of preventative strategies, and provide a useful endophenotype for genetic investigation.

There is some evidence suggesting that reduced P300 amplitude is a stable trait marker in schizophrenia (Mathalon et al., 2000; Blackwood, 2000), with findings of genetic association (Blackwood et al., 2001; Weisbrod, Hill, Niethammer, & Sauer, 1999). However, other results have not been consistent with these findings. For example, in one study, P300 amplitude reduction wasn't found in undiagnosed family members of people diagnosed with schizophrenia (Friedman, Cornblatt, Vaughan, & Erlenmeyer-Kimmling, 1988) nor was it found to be predictive of

subsequent schizophrenic breakdowns (Squires-Wheeler, Friedman, Skodol, & Erlenmeyer-Kimmling, 1993). Because of the relatively low incidence of schizophrenia, even among relatives of those diagnosed with schizophrenia, in the Squires-Wheeler et al. study, as might be expected, there were no more than 6 participants classified as having a schizophrenia-like breakdown and only one met all criteria for schizophrenia (this participant's P300 amplitude was reduced one and a half standard deviations below the mean for the normal group). These findings highlight the need for further confirmation, and for alternative methods to determine whether ERP deficits observed among chronic schizophrenics are trait-like. One such method, included in Study 2 (Chapter 5) comprises a cross-sectional comparison of ERP deficits early (at first presentation) and late (chronic schizophrenia) in the developmental course of schizophrenia.

There have been few studies investigating auditory oddball ERP deficits in people with FESz. Two studies specifically investigated patients at first admission (Demiralp et al., 2002; Salisbury et al., 1998) and a further study (Hirayasu et al., 1998) also included patients whose schizophrenia illness had occurred within one year. All three studies found reduced P300 amplitude, however there were topographical differences between their results. Salisbury et al. found reduced left temporal P300, while Hirayasu et al. and Demiralp et al. found a marked frontal and modest parietal P300 reduction. Of these studies, two (Demiralp et al. & Hirayasu et al.) also examined the N200 component and found both N200 and P300 latencies prolonged in the FESz participants compared to normal controls. Medication status and electrode sites are two factors which may have influenced the different topographical findings. Participants in the Salisbury et al., study were medicated

while participants in the other two studies were unmedicated. The Hirayasu et al. study used T5/T6 electrode sites for their lateral comparison instead of the T3/T4 or TCP1/TCP2 at which left lateralised deficits are usually found (see 4.4). Although the nature of the response required to the target is often considered to affect topography, with the left lateralised deficit more commonly found in the count, than button press response (see 4.4), it is unlikely that response was a confounding factor in this case as all three studies used count rather than button press responses to the target. Other task parameters such as ISI and probability were also consistent across studies and therefore unlikely to affect responses.

Two of these studies did not have large samples, Salisbury et al. with 14 medicated and Demrilap et al., with 12 unmedicated FESz participants, and all three restricted analysis, either to P300 alone (Salisbury et al.) or to N200 and P300 (Demrilap et al. & Hirayasu et al.).

The limitation of these studies to N200 and P300 components, combined with the N100 and P200 component deficits to target and non-target stimuli, found in Study 1 (Chapter3) highlight the need for further investigation of ERPs in FESz. Notably, no studies have examined ERPs to non-target stimuli in FESz. A direct comparison of ERPs in first episode and chronic schizophrenia in a substantial sample, as in Study 2, provides an opportunity to investigate the differences between ERPs at different time points during the course of schizophrenia, i.e. at onset and when illness has become chronic.

The conceptualisation of schizophrenia as a neurodevelopmental disorder and the notion that ERPs might be a biological marker for the condition, suggests that the normal ontogeny of the ERP will be distorted in subjects with schizophrenia. In Study 2, this question of predominantly neurodevelopmental, as against later neurodegenerative change in the cortex, is examined by two methods. The first method is to compare ERP components between both a FESz group and their age and sex matched controls and a chronic schizophrenia group with their controls, to determine if the pattern of deficits found in chronic schizophrenia is present at first onset. The second combines the first episode and chronic groups into one schizophrenia group spanning adolescence to late middle age and similarly combines the younger and older control groups. ERP components from each group are correlated with age, to see if the patterns of age effects differ in the schizophrenia group compared to the control group. This will point to whether changes in ERPs are completed at the time of first presentation, thereby providing some support for the neurodevelopmental hypothesis, or continue to change over time, providing support for a neurodegenerative hypothesis.

#### 4.1.1 Age effects on target and non-target ERP components

The effects of age on the auditory oddball ERP in the normal population have been explored in a number of studies discussed below.

N100 component

Amplitude

Reports of the effect of age on N100 amplitude have been inconsistent. The relationship between N100 and age appears to vary depending upon the stimulus,



with age effects maximal for non-target compared to target stimulus. In a number of studies no relationship between age and N100 amplitude to target stimulus has been found in younger people aged 7-20 years (Johnson, 1989), 4-21 years (Fuchigami et al., 1993) and 11-18 years (Friedman, Brown, Vaughan, & Erlenmeyer-Kimling, 1984). However, in another study, N100 amplitude to targets was found to increase with age in a group 5-19 years (Ladish & Polich, 1989). In adult populations, N100 amplitude to target stimuli has also generally been unchanged in groups aged 18-70 (Bahramali et al., 1998) and 20-79 (Picton, Stuss, Champagne, & Nelson, 1984). Decreased N100 amplitude with age was found in a group aged 18-85 years (Syndulko et al., 1982).

In contrast to target stimuli, N100 amplitude to non-target stimuli has generally been found to increase with age (Anderer, Semlitsch, & Saletu, 1996; Ford & Pfefferbaum, 1991; Pfefferbaum, Ford, Wenegrat, Roth, & Koppell, 1984), although one study reported no effect of age in a group 18-82 years (Iragui et al., 1993).

Several studies (Anderer, Semlitsch, & Saletu, 1996; Ford & Pfefferbaum, 1991; Pfefferbaum, Ford, Wenegrat, Roth, & Koppell, 1984; Iragui et al., 1993; Picton et al., 1984) have examined the effects of age on N100 amplitude topography. These studies have indicated that topography remained stable over age.

#### Latency

N100 latency appears to become earlier with increasing age in the child and adolescent age range, but not in the adult age range. N100 latency to target stimuli has been reported to be earlier with age in groups 4-21 years (Fuchigami et al.,

1993), 8-16 years (Tonquist-Uhlen, Borg, & Spens, 1995) and 5-19 years (Ladish & Polich, 1989). In adults, N100 latency to target stimulus does not show any significant age effects for 17-80 years (Coyle, Gordon, Howson, & Meares, 1991) 15-80 years (Brown, Marsh, & La Rue, 1983) and 18-70 years (Bahramali et al., 1999).

Despite one study to the contrary (Amenado and Diaz, 1998), N100 latency to non-target stimuli, on the other hand, has generally been reported to increase with age in a group aged 18-82 (Iragui et al., 1993) or to show increase at temporal, but not central sites in a group aged 20-88 years (Anderer et al., 1996).

#### P200 component

##### Amplitude

Age changes in P200 amplitude to target stimuli have generally not been found in child or adult groups. P200 amplitude showed no significant change with age for subjects aged 7-20 years (Johnson, 1989), 11-18 years (Freidman et al., 1984), 18-70 years (Baharamali et al., 1999) and 20-79 years (Picton et al., 1984). However, a reduction in amplitude has been reported for ages 18-80 (Smith, Michalewski, Brent, & Thompson, 1980) and for ages 18-85 (Syndulko et al. 1982).

In contrast to target stimuli, P200 amplitude to non-target stimuli has been found to increase with age in ages 20-80 (Anderer, Semlitsch, & Saletu, 1996) and 20-86 (Amenado and Diaz, 1998). Topographic distribution changes evident include higher amplitudes in parietal compared to frontal regions in young subjects, whereas in the elderly the reverse was evident (Anderer et al.). Both these studies had large

sample sizes, with 172 subjects (Anderer et al.) and 73 (Amendeo & Diaz). However no effect of age was reported from 18-82 years in both target and non-target stimuli by Iragui et al. (1993) with a sample size of 71.

#### Latency

P200 latency to target stimuli has been found to decrease with increasing age in young people aged 5-19 years (Ladish & Polich, 1989), but to either increase with age to non-target stimuli in adult groups (Goodin, Squires, Henderson, & Starr, 1978; Polich et al., 1995) or show no difference (Brown et al., 1983) with age. Anderer et al. (1996) have suggested that the delay may depend on the site, occurring at anterior but not posterior sites because in his study found that P200 was earliest at Fz in the elderly but was delayed at Fz in the young group.

#### N200 component

##### Amplitude

N200 amplitude to target stimuli has been found to decrease with increasing age in young groups 5-19 years (Ladish & Polich, 1989) and 4-16 years (Enoki et al., 1993). However, Fuchigami et al. (1993) failed to find a decrease in a group 4-21 years. The amplitude of N200 has also been reported to be decreased in adults aged 18-82 years (Iragui et al., 1993), and 20-88 years (Anderer et al., 1996) or unchanged (Amenedo et al., 1998; Brown et al., 1993; Picton et al., 1984) with age.

#### Latency

N200 latency has been reported to decrease with age in groups 4-21 years (Fuchigami et al. 1993) and 5-19 years (Ladish & Polich, 1989). Enoki et al., (1993) reported a significant decrease in children and adolescents (9.03 msec/year) reaching

its minimum latency at age 16, and then changing to a slight but significant increase in latency with age (0.97ms/year) through to 77 years. In adult groups N200 latency has been found to be prolonged with age in many studies; with an increase in latency of .065msec/year from 20-79 years (Picton et al., 1984); 0.8msecs/year from 16-76 years (Goodin et al., 1978), 0.58 msec/year (Iragui et al.), 0.25msec/year from 20-88 (Anderer et al., 1996).

### P300 component

#### Amplitude

The relationship between age and P300 amplitude has been inconsistent in studies with young people, which may reflect the possibility that changes in probability and other task demands may interact with age to affect results. For example, a decrease in P300 amplitude at Pz from 7-20 years (1.11  $\mu\text{v}/\text{year}$ ) has been found in a reaction-time version of the oddball task, but not in the count version of the oddball task (Johnson, 1989). P300 amplitude increased from 4-20 years at Fz (4.6  $\mu\text{v}/\text{year}$ , Cz (2.6  $\mu\text{v}/\text{year}$ ) and Pz (4.1  $\mu\text{v}/\text{year}$ ) in a low probability condition (10% target) and at Pz only (8.4  $\mu\text{v}/\text{year}$ ) in a high probability condition (30% target) in a study using finger movement to respond to the target stimulus (Polich, Ladish, & Bums, 1990). No age effects on P300 amplitude were found in a group aged from 4-21 years using a button press response (Fuchigami et al., 1993)

In studies with adults, decreases in P300 amplitude with increasing age have been found in a number of studies. For example, a decrease of 0.18  $\mu\text{v}/\text{year}$  from 20-79 years (Picton et al., 1984); 0.15  $\mu\text{v}/\text{year}$  from 15-80 years (Brown et al., 1983); 0.1  $\mu\text{v}/\text{year}$  from 18-82 years, (Iragui et al., 1993); and 0.47 V from 20-88 years

(Anderer et al., 1996). This relationship may also interact with gender as Amendio and Diaz (1998) found that age affected P300 amplitude in men, but not in women. P300 amplitude has also been found to be more frontally oriented with age in some studies (Anderer et al., 1996; Ford & Pfefferbaum, 1991; Picton et al., 1984).

### Latency

P300 latency has been consistently found to increase with age. This effect has been found amongst studies that included young (6-15 years, Goodin et al., 1978; 6-23 years, Martin, Barajas, & Fernandez, 1988), or adult (Iragui et al., 1983; Picton et al., 1984) subjects only, and in studies including both young and adult populations (5-86 years Polich, Howard, & Starr, 1985). With regard to this slowing of P300 among adults, delays from 0.53 to 2.45 msec/year have been found as follows: for example, an increase of 1.36 msec/year from 20-79 years (Picton et al., 1984), 1.8 msec/year from 16-76 (Goodin et al., 1978), 2.45 msec/year from 18-90 years (Pfefferbaum et al., 1984), 0.53 msec/year for subjects over 45 years (Brown et al., 1983), 0.80 msec/year from 18-82 years (Iragui et al., 1993), 0.92 msec/year from 20-88 years (Anderer et al., 1996) and 0.82 msec/year from 20-86 (Amenedo & Diaz, 1998). Accelerated rates of slowing have also been reported in elderly subjects aged from 70-88 years and also in subjects 63 years of age and over (Gordon, Kraiuhin, Stanfield, Meares et al., 1986).

### Summary of age effects on ERPs

To summarise, the effects of increasing age on ERPs to non-target stimuli are: an increase and delay in N100 amplitude and an increase in P200 amplitude. The effects of increasing age on ERPs to target stimuli are: earlier P200 latency to target

stimuli, an initial decrease in childhood, till around 16 years, and then decrease in adulthood of N200 amplitude; a prolongation of N200 latency; and a decrease and delay in P300.

#### 4.1.2 Gender effects on ERPs to target and non-target stimuli

Attempts to explain and integrate the heterogeneity of research findings in schizophrenia have mostly focussed on symptom factors (see Chapter 4.2). An additional approach is the examination of gender differences (See Chapter 1.2.1) suggesting that men and women are prone to different subtypes (Castle & Murray, 1993; Goldstein, Santangelo, Simpson, & Tsuang, 1990; Murray, O'Callahan, Castle, & Lewis, 1992).

Few studies have examined gender effects on ERPs in schizophrenia. ERP studies (Hirayasu et al., 1998; Josiassen, Roemer, Johnson, & Shagrass, 1990; Turetsky, Colbath and Gur, 1998) which have found gender differences, suggest that it may not be sufficient to control for gender by matching control and patient participants, as the effects of gender may be different in schizophrenia. For this reason, Study two has examined the gender differences found in control *and* schizophrenia groups to see if there is a different pattern in the schizophrenia group compared to the control group. Turetsky et al., for example, found differences in the profile and severity of P300 deficits for men and women with schizophrenia, with women showing greater left temporal and frontal P300 deficits while men had greater right parietal P3 deficits. This pattern of gender differences was not found in the control group. Hirayasu et al. included gender as a factor in the analysis of N200,

P300 components, and found earlier N200 latency in females compared to males in the control and medicated schizophrenia group, but not in a neuroleptic naïve group. In addition, increased P300 amplitude in females compared to males in both clinical and control groups was evident. Even in normal groups, ERP gender differences have not been clearly explicated. Again the focus has been on gender effects on the P300 component, with males having a reduced (Deldin, Duncan, & Miller, 1994; Hoffman & Polich, 1999; Polich & Geissler, 1991 although see Shelton, Hartmen, & Allen, 2002) and prolonged (Deldin et al., Golgeli et al., 1999; Polich, Burns, & Bloom, 1988; Shelton et al., 2002) P300 component compared to females. These findings highlight the need to explore the modulatory effects that gender may have on ERPs in first episode and chronic schizophrenia

#### 4.2 EFFECTS OF SEQUENTIAL POSITION OF NON-TARGETS ON ERPs.

ERPs are averaged to increase the signal to noise ratio of small stimulus related responses from the background EEG activity. The underlying assumption is that the response elicited by all occurrences of an event (e.g., either target or non-target stimuli) are identical or of little consequence. However, this assumption has been challenged by findings of systematic trial to trial variations in response to both target and non-target stimuli (Squires, Wickens, Squires, & Donchin, 1976; Hermanutz, et al., 1981). Typical analyses of ERPs elicited by target and non-target stimuli averages obscure these variations. Study 2 will examine the relationship between certain specific sequence effects and non-target stimuli and Study 3 (Chapter 6) will examine the sequence effect of preceding stimuli on ERPs elicited by targets.

In non-target sequence studies the non-target immediately before and after the target stimuli are referred to with various nomenclatures. For simplicity of expression the terminology used by Starr, Sandroni and Michalewski, (1995) will be followed in this thesis, with the non-target immediately preceding the target referred to as *T-I* and the non-target immediately following the target referred to as *T+I*. ERPs may be influenced by the momentary brain state at stimulus presentation (Bani, de Pascalis, Hodder, Clarke, & Johnstone, 2003; Basar, Basar-Eroglu, Rosen, & Schutt, 1984), which in turn may be affected by the category of the previous stimuli (target or non-target, match or mismatch). For example, the processing of a target stimulus may activate additional, transient neural processes that operate on *T+I* stimuli (Hirata & Lehman, 1990). There is also the possibility of a difference in preparedness associated with the predictability of the *T+I* stimulus, in those oddball designs in which a target stimulus is always followed by a non-target stimulus, either by constraint or by nature of the low probability of target stimuli. In this case efficient information processing would involve reduced allocation of attention to a stimulus known to occur at a particular position, *T+I*, while there would be more active processing of the more salient *T-I* stimulus which could be either a target or non-target stimulus.

Non-target sequence effects have also been investigated according to the number of preceding non-target stimuli (Hermanutz et al., 1981) with results showing that N100 amplitude increases with an increasing number of preceding non-targets. This is an intriguing finding when contrasted with habituation findings in N100 amplitude (Budd, Barry, Gordon, Rennie, & Mitchie, 1998; Fruhstorfer, 1971; Ritter, Vaughan, & Costa, 1968). However, whereas habituation studies generally



have task instructions to ignore the stimuli, the non-target sequence results have been found with paradigms in which a response to target stimuli is required. The increasing N100 amplitude with the number of preceding non-targets could thus reflect progressively increasing vigilance for the target stimulus.

In Study 2, ERPs to both T-1 and T+1 stimuli are averaged separately. The Gray-Hemsley model and other conceptualisations of schizophrenia as a failure to make use of context in information processing (Chapter 1) would suggest that the preparedness for the T+1 stimulus would be impaired in participants with schizophrenia, as they would fail to make use of previous regularities, i.e. that a target is always be followed by a non-target to make redundancies in information processing.

Empirically, in the few studies in which ERPs to non-target stimuli have been sub-averaged according to their temporal position to the target stimuli (immediately preceding or immediately following) significant differences have been found in normal samples (Hirata & Lehman, 1989; Roth & Cannon, 1972; Starr, Sandroni, & Michalewski, 1995; Starr, Aquinaldo, Roe and Michalewski, 1997). In each of these studies the target stimulus was always followed by a non-target stimulus. These studies found N100 amplitude (or its equivalent maximal potential range in the Hirata and Lehman study) reduced to T+1 compared to T-1 stimuli in normal subjects. However the Starr, Aquinaldo et al. study only found N100 reduced to T+1 in button press, but not count response condition; while Hirata & Lehman found a reduction with mental count. However, this reduction was not present in a schizophrenia group (Roth & Cannon) or in a group with Alzheimer's disease or

their elderly controls (mean age 66.3 ± 1.6; Golob & Starr, 2000). The N100 component to *T+1* was also delayed in latency, and decreased in global field power and current source density compared with the *T-1* N100 (Hirata & Lehman).

Compared to the *T+1* stimulus, the *T-1* P200 component was reduced in amplitude (Starr, Aguinaldo et al., 1997) and occurred earlier. Starr, Sandroni et al. (1995) found a pre-stimulus negative shift (RP) and P300 component to *T-1* stimuli, which were both absent to *T+1* stimuli and *T-1* P50 amplitude was reduced compared to *T+1* stimuli. Hirata and Lehman (1990) concluded that an average of all non-target stimuli should be avoided as they involved distinctly different ERP characteristics, which the authors interpreted as manifestations of different brain states.

The reduction in N100 amplitude to *T+1* compared with *T-1* stimulus in normal subjects was consistent across studies, despite differences in task instructions and analyses. For example, in the Roth & Cannon study the instructions were to ignore the stimuli as much as possible while the remaining studies all required a response to the target stimuli, Starr et al. (1995,97) compared two response conditions (button press and count) and the Hirata & Lehman (1990) study used a mental count response.

#### 4.3 SENSITIVITY OF ERP DEFICITS FOR SCHIZOPHRENIA

Research has demonstrated a widely reproducible, reduced P300 amplitude in schizophrenia (Ford, 1999; Jeon & Polich, 2000; Pritchard, 1986). Previous literature has focused on the sensitivity of the P300 component in schizophrenia, the

classification of patients with schizophrenia from normal controls. For example, Ford, Pfefferbaum & Roth (1992) established criterion P300 amplitude, above which a diagnosis of schizophrenia may be excluded. Most have focused on P300 amplitude to the target stimulus. Boutros et al. (1997) however, found that non-target N100 and P200 components were also sensitive measures and recently Ford (2001) proposed that N100 amplitude reduction to target and non-target stimuli may not only be sensitive for schizophrenia, but may also have greater specificity (i.e. the extent to which this deficit is not present in persons without schizophrenia, in including those with non-schizophrenic psychiatric disorders) for schizophrenia than P300 reduction. In that study, while P300 amplitude was sensitive to schizophrenia-like symptoms found both in schizophrenic and in epileptic patients with interictal chronic schizophrenia-like features, only N100 amplitude reduction was specific to those symptoms in schizophrenia.

Study 2 investigates the sensitivity of the N100 and P200 components elicited by non-targets and targets and compares this to the P300 component to targets in discriminating chronic schizophrenia and FESz groups from their respective normal control groups. It can be seen that the rationale for examining whether discriminant function analysis of N100 and P200 components to target stimuli and non-target stimuli, separately to *T-1* and *T+1* stimuli shows greater sensitivity for schizophrenia than P300 amplitude includes both theoretical and empirical reasons. The results of Study 1 (see Chapter 3) indicate that there is a reduced difference between target and non-target N100 and P200 scores in a schizophrenia group. The results of Roth and Cannon's early study demonstrated reductions in N100 amplitude to *T+1* compared with *T-1* stimuli in normal control subjects but not in schizophrenia. There is also a

theoretically based prediction that there would be reduced processing of  $T+1$  compared with  $T-1$  stimuli in normal controls but not in schizophrenia.

#### 4.4 ERP TOPOGRAPHY IN SCHIZOPHRENIA

Topographical variations in ERP component measures in schizophrenia may have diagnostic (Gruzelier et al., 1999; Maurer, Riederer, Heinsen, & Beckmann, 1989; Salisbury, Shenton & McCarley, 1999; Weir, Fiaschi & Machin, 1998) and pathophysiologic (McCarley et al., 1989, 1993; O'Donnell et al., 1995, 1999) significance. Most studies of ERP topography in schizophrenia have restricted their investigation to the topography of the P300 component with several studies showing a left lateralised amplitude reduction in schizophrenia compared to normal controls (e.g., Faux et al., 1990, 1993; Faux, Torello, McCarley, Shenton, & Duffy, 1988; Morstyn, Duffy, & McCarley, 1983; Potts, Hirayasu, O'Donnell, Shenton & McCarley, 1998; Salisbury, Shenton, & McCarley, 1999). This has also been found to be present at first onset by some studies (Demiralp et al., 2002; Salisbury et al., 1998). However, the robustness of these findings is challenged by other studies which have not found this difference (Ford et al., 1994; 2000; Hirayasu et al., 1998; Iwanama et al., 2002; Pfefferbaum, Ford, White, & Roth, 1989).

There are several possible explanations for the variable findings. A meta-analysis of 11 topographic studies of P300 amplitude elicited by the auditory oddball, in schizophrenia, indicated the importance of electrode site placement with greater effect sizes found using TCP1/TCP2 sites than T3/T4 (Jeon & Polich, 2001). Task requirements have also been found to influence results with inter-hemispheric differences more prevalent in tasks requiring silent counting of targets compared to button press. However, investigations comparing button press and count in the same

schizophrenia and normal control groups have been conflicting. For example, Ford, Mathalon, White and Pfefferbaum (2000) did not find smaller P300s over the left (T3) than over the right (T4) lateral scalp in the schizophrenia group, in both button press and silent count, while Salisbury, Rutherford, Shenton, McCarley (2001) found left lateralised deficit in the silent count condition, but not in the button press condition in another schizophrenia group. Turetsky et al. (1998) demonstrated a left temporal deficit in schizophrenia, using the button press. Stimulus discriminability has also been found to influence topographical results, with asymmetrical findings in schizophrenia associated with easier discrimination of pitch tone (Salisbury et al., 1994; Weisbrod et al., 1997). It is also possible that patient differences, for example, variable structural deficits, may have contributed to the conflicting results.

Potts et al. (1998) also investigated the topography of N100 amplitude and found no topographic difference between the schizophrenia and control groups. Study 2 investigates laterality and anterior/posterior differences in topography of all target and non-target ERP components in first episode and chronic schizophrenia groups compared to normal controls.

#### 4.5 SYMPTOM INTERACTIONS WITH ERPs

Consideration of symptom factors can reveal significant associations with brain function that can be obscured through averaging across subgroups of the disorder (Harris et al., 2001; Liddle, 1987, 1992; Liddle et al., 1992; Williams, Gordon, Wright, & Bahramali, 2000; Williams et al., 2003). Chapter one reviewed the heterogeneity of schizophrenia symptoms and their organisation into factors. Three syndromes or factors (Liddle, Barnes, Morris, & Hague, 1989): reality

distortion, psychomotor retardation and disorganisation, (also called positive, negative and disorganisation factors in some studies, with minimal item differences), have been replicated extensively in factor analytic studies, even when additional factors have also been found (Andreasen, Arndt, Alliger, Miller, & Flaum, 1995; Bell et al., 1994; Hori et al., 1999; Johnstone & Frith, 1996; Lenzenweger & Dworkin, 1996; Malla, Norman Williamson, Cortez, & Diaz, 1993; Maziade et al., 1995; Minas, Klimidis, Stuart, Copolov, & Singh, 1994; Murphy, Burke, Bray, Walsh, & Kendler, 1994; Peralta, Cuesta, & Fariñas, 1997; Ratakonda, Gorman, Yale, & Amador, 1998; Thomson & Meltzer, 1993) including recent onset psychosis studies (Gureje, Deribigbe, & Obikoya, 1995; Van de Does, Dingemans, Linszen, Nugter, & Scholte, 1996; Vazquez-Barquero et al., 1996 - with 2 positive; but see McGorry, Bell, Dudgeon, & Jackson, 1998 & Van Os et al., 1996 who found different factor structures in FESz).

Most studies which relate psychophysiological, neurocognitive and neuroanatomical structural and functional findings to symptom factors (Baxter & Liddle, 1998; Brown & White, 1992; Chua et al., 1997; Harris et al., 2001; Higashima et al., 1998; Liddle, 1987, Liddle & Morris, 1991; Liddle et al., 1992; Norman et al., 1997a, 1997b; Schroder et al., 1992, 1995) limit these factors to these three core symptom factors. Although five or more factors can be obtained with the addition of the general psychopathology scale of the PANNS, the three factors have been shown to adequately account for the heterogeneity of the core schizophrenic symptoms. Other studies have only used two subgroups, for example, active and withdrawn (Gruzellier et al., 1999), positive and negative (Laurent et al., 1999). There are 14 items each in the Positive and Negative subscales of the PANSS, the

inclusion of the general psychopathology scale, which adds an additional 14 items would require a sample size of more than 120 patients with schizophrenia to meet the minimum subject to variable ratio requirements, while the sample size of most EEG, sMRI, fMRI and SPECT studies would preclude the use of principal component factor analysis with this number of items.

Because of the relative reliability of the three factor solution derived by Liddle (1987) and to allow direct comparison with other psychophysiological studies (e.g. Norman et al., 1997; Harris et al., 2001; Higashima et al., 1998; Kawasaki et al., 1997) correlations in Study 2 are based on Liddle's three factor solution: disorganisation, psychomotor poverty and reality distortion. This allows a comparison between the first episode and chronic groups in Study 2. The scores for the three factors were obtained by summing up PANS S scores according to the item structure of Liddle's factor analysis (Cuesta & Peralta, 1995; Liddle, 1992, Shean, 1999; See Chapter 5, Table 5.3 for item structure).

#### Disorganisation

The disorganisation factor, reflecting thought disorder or cognitive impairment, has been assumed to represent the core feature of schizophrenia (Higashima et al., 1998). It has been found to be correlated with patients with a familial history of schizophrenia (Cardno, Rijdsdijk, Sham, Murray, & McGuffin 1997; Loffler and Hafner, 1999; Loftus, Delisi, & Crow, 1998), the highest neurological soft-signs scores (Arango, Kirkpatrick and Buchanan, 2000; Schroder et al., 1992) and putative psychophysiological markers such as smooth pursuit eye movement (SPEM) dysfunction (Lee and Williams, 2000; Lee, Williams, Loughland,

Davidson, & Gordon, 2001). High scores on this factor have been associated with poor performance in tasks which involve using context in information processing or the ability to inhibit irrelevant mental activity, as when the subject is required to: inhibit an established but inappropriate response (Liddle and Morris, 1991), suppress irrelevant verbal responses (Baxter and Liddle, 1998), use inhibition in a verbal fluency task (Cohen, Barch, Carter and Servan-Schreiber, 1999), inhibit proactive interference (Guillem, Bicu, Bloom, Wolf, Desautels et al., 2001), combine context related stimuli (Silverstein, Kovacs, Corry, and Valone, 2000), and by showing reversed negative priming (Williams, 1996) and perseveration on a test of set shifting ability (Cohen et al., 1999).

Structural studies (MRI and CT) have either not found a relation between disorganisation and structural deficits (Flaum et al., 1995; Malla, Takhar, Norman, & Assis, 1999; Mozley et al., 1994) or have found a relationship with increased third and lateral ventricles and ventricle:brain ratio (Schroder, Buchsbaum, Siegel, Geider, & Niethammer, 1995) or increased bilateral parahippocampal grey cortex volume (Chua et al., 1997). Disorganisation has been more robustly associated with functional compared with structural changes, a pattern of results that suggests a widespread abnormality of function consistent with disconnectivity models (see Chapter 1). In functional imaging studies (PET and SPECT) disorganisation has been associated with increased anterior cingulate activity (Liddle et al., 1992; Schroeder et al., 1996; Yuasa et al., 1995) and decreased activity in the right ventrolateral prefrontal cortex and right and left angular gyms (Liddle, Friston, Frith, Hirsch, Jones and Frackowiak, 1992).



#### 4.5.1 Psychomotor Poverty

Psychomotor poverty has been associated with: slowing of mental activity (Baxter & Liddle, 1998; Bilder, Mukherjee, Rieder, & Pandurangi 1985; Johnson & Frith, 1996; Liddle & Morris, 1991; Sauer et al., 1999; Van der Does, Dingemans, Linszen, & Nugter, 1996), tasks that require planning abilities (Brown & White, 1992; Himelhoch, Taylor, Goldman, & Tandon, 1996), memory - both long term and procedural (Norman et al., 1997; Schroeder, Tittel, Stockert, & Karr, 1996), and poor conceptual thinking (Bilder et al., 1985; Liddle, 1987). Differing patterns of structural and functional abnormalities have been associated with psychomotor poverty, the most consistent a relationship with frontal lobe structural abnormalities (Chua et al., 1997; Schroder et al., 1992, 1996; Liddle et al., 1992; Schroder et al., 1996; Woodruff et al., 1997). The psychomotor poverty or negative dimension is thus associated with a loss of function and is correlated both with the existence of pre-morbid abilities (Sauer et al., 1999) and with eventual outcome (Carpiniello & Carta., 2002; Weisलगren, Lindstrom, & Lindstrom, 1996).

#### 4.5.2 Reality Distortion

Reality distortion (or the positive/psychotic factor) has not been reliably correlated with neurocognitive measures, with a large number of studies failing to demonstrate a significant association (Brown & White, 1992; Frith, Leary, Cahill, & Johnstone, 1991; Gureje et al., 1995; Liddle & Morris, 1991; Sauer et al., 1999; Van der Does et al., 1993). However, a few studies have indicated an association between reality distortion and performance on tests of recognition and logical memory (Johnstone & Frith, 1996; Norman et al., 1997; Schroeder et al., 1996). Reality

distortion has also been associated structurally (NIRI & CT) with increased interhemispheric fissure (Schroder et al., 1995).

#### 4.5.3 Psychophysiology and symptom factor

In resting EEG, reality distortion has been associated with reduced frontal-temporal EEG coherence (Norman et al., 1997) and psychomotor poverty has been associated with increased levels of frontal slow wave activity (Gerez & Tello, 1995; Gattaz et al., 1992; Harris, Williams, Gordon, Bahramali, & Slewa-Younan, 1999). Correlations with P300 have not been consistent. Some studies have found no significant correlations between P300 and clinical symptoms (Pritchard, 1986) while others have found relations between P300 amplitude and both negative (Blackwood et al., 1987; Eikmeier, Lodemann, Zerbin, & Gastpar, 1992; Pfefferbaum, Ford, White & Roth, 1989; Strik, Dierks, & Maurer, 1993) and positive symptoms (Egan et al., 1994; McCarley et al., 1989; Shenton et al., 1989). Disorganisation has been associated with reduced P200 amplitude and delayed N100 latency to non-target stimuli (Williams, Gordon, Wright, & Bahramali, 2000).

## 4.6 OBJECTIVES FOR STUDY 2

1. To clarify whether target and non-target ERP deficits are present among participants with FESz and chronic schizophrenia.
2. To determine if a combination of target and non-target ( $T-I$  &  $T+I$ ) ERP deficits can enhance prediction of diagnostic status derived solely from the P300 deficit to targets.

3. To determine if non-target sequence effects ( $T-1$  &  $T+1$ ) found in normal groups are present in first episode and chronic schizophrenia.
4. To explore the relationship between ERP findings and clinical variables, especially clinical symptoms.
5. To examine maturational effects on ERPs to target and non-target ERPs in schizophrenia and normal controls.
6. To examine gender effects on ERPs to target and non-target ERPs in schizophrenia and normal controls.
7. To examine topographical differences between the groups with schizophrenia and their control groups.

## 5 STUDY 2 - ERPs TO TARGET AND NON-TARGET (BEFORE & AFTER TARGET) STIMULI: FIRST EPISODE VS. CHRONIC SCHIZOPHRENIA

The purpose of this Study was to examine target and non-target (T-1 & T+1) ERP disturbances in first episode and chronic schizophrenia. The main results have been published (Brown, Gonsalvez, Harris, Williams, & Gordon, 2002, see Appendix 2 for a copy of this article). A more complete account of the Study and its results is presented below.

### 5.1 HYPOTHESES

Compared to age and sex matched controls, chronic and FESz groups will show similar patterns of target and non-target ERP disturbances. Specifically:

#### a) Non-targets (*T-1* & *T+1*)

1. N100 will be reduced to *T-1* and *T+1* stimuli in the schizophrenia groups.
2. P200 will be reduced and early to both T-1 and to T+1 stimuli in the schizophrenia groups.

#### b) Targets

1. N100 will be reduced and earlier to target stimuli in the schizophrenia groups.
2. P200 will be increased and delayed to target stimuli in the schizophrenia groups.
3. N200 and P300 will be reduced and delayed to target stimuli in the schizophrenia groups.

c) Between-stimuli

1. N100 will be increased to target compared with non-target stimulus in the control but not the schizophrenia groups.
2. N100 will be increased to *T-I* compared with *T+I* stimuli in the control but not the schizophrenia groups.
3. P200 amplitude will be increased and prolonged to non-target compared with target stimuli in the control but not the schizophrenia groups.
4. P200 amplitude will be increased and prolonged to *T-I* compared with *T+I* stimuli in the control but not the schizophrenia groups.

d) Gender effects on ERPs

There will be an interaction between gender and groups. Specifically it is hypothesised that males will show greater deficits than females in the schizophrenia group.

e) Age effects on ERPs

In comparison to the control group, age effects on ERP components will be diminished (support for neurodevelopmental hypothesis) rather than enhanced (support for neurodegenerative) hypothesis in the schizophrenia group. Specifically:

1. N100 amplitude to non-target stimuli will increase with age in the control, but not the schizophrenia groups.
2. P300 will be reduced and delayed with age in the control, but not the schizophrenia groups.

f) Symptom effects on ERPs

ERP deficits in schizophrenia will be related to clinical symptoms, particularly severity of thought disorganisation.

g) Sensitivity for schizophrenia

Inclusion of variables derived from non-target ERPs such as N100 and P200 components will improve classification rates for both first episode and chronic schizophrenia than classification using only target parameters (N200/P300).

## 5.2 METHOD

### 5.2.1 Participants

#### 5.2.1.1 Participants with chronic schizophrenia

Forty<sup>1</sup> participants with chronic schizophrenia, aged between 23 and 51 years of age, with a mean age of 36.0 years (SD = 7.1 years) were recruited from inpatient (both acute and long stay) and community settings in the western suburbs of Sydney (see Table 5.1 for demographic and clinical information). Diagnosis was confirmed using Section G (schizophrenia and psychotic disorders) of the Composite International Diagnostic Interview (World Health Organisation, 1992a) or by two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM — IV: American Psychiatric Association, 1994). Although chronic schizophrenia is defined as a period of symptomatic illness lasting for greater than two years, all participants had been diagnosed with schizophrenia for a minimum

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<sup>1</sup>Twenty five of these were subjects included in Study 1. An additional 15 subjects were acquired to meet chronicity requirements.

period of at least four years (range 4 -34 years) with a mean duration of illness of 14.3 yrs (SD = 7.0 yrs). All patients were medicated and details about medication are

Table 5.1 Demographic and clinical variables of chronic schizophrenia and FESz participants.

Chronic schizophrenia	Male (n=26)		Female (n=14)		Total (n=40)	
	Mean	sd	Mean	sd	Mean	sd
Age (yrs)	36.4	6.3	35.4	8.7	36.0	7.1
Illness duration (yrs)	15.1	7.2	12.7	6.8	14.3	7.0
Chlorpromazine equi	568	471	431	312	520	423
Years of education	11.72	2.2	11.27	2.5	11.57	2.3
PANSS scores						
Positive symptoms	20.5	7.0	19.9	5.5	20.3	6.5
Negative symptoms	21.0	6.5	19.9	6.6	20.6	6.5
General symptoms	37.2	8.4	38.3	8.4	37.6	8.3
Total	78.7	19.5	78.1	17.9	78.5	18.7
First episode schizophrenia	Male (n=28)		Female (n=12)		Total (n=40)	
	Mean	sd	Mean	sd	Mean	sd
Age (yrs)	19.7	2.7	19.5	4.4	19.6	3.2
Chlorpromazine equi	262	215	222	173	250	202
Years of education	11.5	1.8	11.2	2.1	11.3	1.9
PANSS scores						
Positive symptoms	17.8	5.9	15.3	4.6	17.2	5.7
Negative symptoms	21.0	6.2	15.9	4.6	19.5	6.2
General symptoms	39.3	6.9	37.3	6.8	38.7	6.9
Total	78.1	14.6	68.5	14.8	75.2	15.1

Table 5.2 Medication

	Chronic schizophrenia						FESz					
	Males (n=26)		Females (n=14)		Total (n=40)		Males (n=28)		Females (n=12)		Total (n=40)	
	n	%	n	%	n	%	n	%	n	%	n	%
Nil Medication	0	0	0	0	0	0	4	14	0	0	4	14
Antipsychotics												
-typical	15	58	5	36	20	50	0	0	0	0	0	0
-atypical	5	19	3	21	8	20	23	82	12	100	36	86
-clozapine	7	27	6	43	13	33	1	27	0	0	1	3
Antipsychotics alone	15	58	8	57	23	58	19	68	9	75	28	70
Antidepressants	1	4	4	29	5	13	3	11	1	8	4	10
Anticholinergics	8	31	2	14	10	25	3	11	1	8	4	10
Anticonvulsants	3	12	0	0	3	8	0	0	0	0	0	0

included in Table 5.2 Exclusion criteria were a recent history of substance abuse, past history of substance dependence, mental retardation, and other neurological disorders including epilepsy and head injury (defined as an injury requiring hospital observation for at least 4 hours or unconsciousness for greater than one hour).

#### 5.2.1.2 Participants with FESz

Forty people with FESz aged between 14 yrs and 26 yrs (mean = 19.6 yrs; SD = 3.2 yrs), were recruited from community and hospital settings through the Western Sydney First Episode Psychosis Project (see Table 5.1 for clinical and demographic variables). Young people, presenting for the first time to health services, with psychotic symptoms that warranted a diagnosis of either schizophrenia or schizophreniform disorder were included. Diagnosis was made by means of a consensus conference (of at least three fully qualified psychiatrists) that drew upon information from a clinical interview by the participating psychiatrist, information from family and case manager and the case notes. Diagnoses were made according



to the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM - IV) (American Psychiatric Association, 1994). Exclusion criteria were the same as that for the chronic group. The majority of participants were medicated with atypical antipsychotics alone ( $M=250$  chlorpromazine equivalents:  $SD = 202$ ), though a small number were also receiving antidepressant or anticholinergic medications (see Table 5.2 for details of medication). Four participants were not on medication.

#### 5.2.1.3 Positive and Negative Symptom Scale (PANSS)

Schizophrenic symptoms for both chronic and FESz groups were rated, using the Positive and Negative Syndrome Scale (PANSS., Kay and Opler, 1987) by the interviewing psychiatrist on the same day as the data acquisition (see Table 5.1).

#### 5.2.1.4 Normal control participants

Normal control participants for the two groups were recruited from the community and were age and gender-matched to within 2 years of the ages of their clinical counterparts under the age of 25 years, and to within 5 years for those over the age of 25 years. The rationale for closer age-matching of the younger participants derived from research indicating maturational changes in the EEG/ERP, occurring up to early adulthood (Niedermeyer, 1999; also see Chapter 4.1.1). The older control group, with a mean age of 36.7 yrs ( $SD = 7.6$ ), was compared with the chronic schizophrenia group, and the younger control group, with a mean age of 19.65 yrs ( $SD = 3.86$ ), was compared with the FESz group. Persons with a recent or past history of mental illness, epilepsy, other neurological disorders, mental

retardation or head injury were excluded from the sample as were persons with a recent history of substance abuse, or past history of substance dependence.

### 5.3 PROCEDURE AND DATA ACQUISITION

After first obtaining voluntary consent, participants were interviewed using a semi-structured interview schedule and were questioned about their previous psychiatric history, family psychiatric history, medical history and level of educational attainment. The PANSS was also administered at this time. All participants were asked to refrain from smoking or drinking caffeine for three hours prior to testing. The Study was approved by Western Area Health Service and University of Wollongong ethics' committees. The task used and procedures for data acquisition were the same as Study 1 (see Chapter 3.2.2 p 53). Additionally, ( $T-I$ ) non-targets which occurred immediately before the target were averaged separately from ( $T+1$ ) non-targets which immediately followed the target tone. For targets N100, P200, N200 and P300 peaks were measured relative to a prestimulus (200ms) baseline by an automated system based on the detection of a consistent change in the direction of the gradient of the waveform (Haig et al., 1995). Thus a change from a consistently positive to a consistently negative gradient was identified as a positive peak, and vice versa for a negative peak. Although a 100 ms epoch is used for analysis graphs shown in this thesis are contracted to show 100ms before and 700 ms post stimulus, as all ERP components occur within this window and it allows the most efficient use of space in the figures. The time window for N100 was set at 80 - 140ms, for P200 between 150-240ms, for N200 between 200-280ms and for P300 between 250-500 ms. Components were scored at all 19 sites (Fp1, Fp2, Fz, F3, F4,

F7, F8, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, 01, 02) according to the 10-20 International system (Bloom, 1982) in reference to linked-ear electrodes.

## 5.4 ANALYSIS

Analysis is considered under three main sections, midline ERPs, topography and response time. The Statistical Package for Social Sciences 10.0 program (SPSS Inc., 1999) was used in all analyses.

### 5.4.1 Midline ERPs

#### 5.4.2 Clinical vs. control groups

N100 and P200 amplitudes and latencies were submitted separately to a 4-way ANOVA repeated measures design, incorporating group (schizophrenia vs. controls) by gender (male vs. female) by stimuli (T-1, target and T+1) by electrode site (Fz, Cz, Pz) with repeated measures for electrode site and stimulus factors. For the stimulus factor, two specific planned contrasts were carried out: (i) target vs. non-targets (T vs. T-1/T+1), to examine whether the target status influenced ERP components, and (ii) between non-targets (T-1 vs. T+1), to examine whether the sequential position of the non-target affected ERP components. For the site factor, linear and quadratic contrasts were examined, the linear contrast purporting to examine reduced amplitudes at parietal sites (Fz vs. Pz) and the quadratic contrast purporting to test the frequently observed maximal amplitudes at central sites (Cz vs. Fz + Pz).

N200 and P300 components were reliably observed only to the target stimulus and were therefore subjected to a 3-way ANOVA incorporating group (schizophrenia vs. controls) by gender (male vs. female) by site (Fz, Cz, Pz), with repeated measures for the site factor. Similar linear and quadratic contrasts as described above were conducted for the site factor. These analyses were done separately for the chronic schizophrenia group vs. older controls and the FESz group vs. younger controls.

#### 5.4.2.1 Effects of age on ERPs

Pearson's two-tailed correlations between age and all component amplitudes and latencies at the site at which the component was maximal (N100 and P200 at Cz, N200 at Fz and P300 at Pz) were performed separately for the combined control group and the combined schizophrenia group.

#### 5.4.2.2 Effects of clinical symptom on ERPs

This analysis was based on the three factor structure (see Table 5.3) identified by Liddle (Cuesta & Peralta, 1995; Liddle, 1982, Shean, 1999).

Table 5.3 PANS S items included in each factor

<u>Reality Distortion</u>		Psychomotor poverty		Disorganisation	
P1	Delusions	N2	Emotional withdrawal	P2	Conceptual disorganisation
P6	Suspiciousness	N4	Passive/apathetic social withdrawal	N7	Stereotyped thinking
P3	Hallucinatory behaviour	N6	lack of spontaneity	N5	Disorientation and difficulty in abstract thinking
		G7	Motor retardation		

Pearson's two-tailed correlations between symptom factors and component amplitudes and latencies at the site at which the component was maximal (N100 and P200 at Cz, N200 at Fz and P300 at Pz) were performed separately for chronic and FESz groups.

#### 5.4.2.3 Classification of subjects into diagnostic groups

The accuracy with which ERP components could be used to classify subjects into their respective diagnostic groups was examined by discriminant function analysis (DfA). Two separate stepwise DfA were performed: the first to determine the classification rate derived from the early components (N100 and P200) elicited by target and non-target stimuli; and the second, to determine whether classification rates improved with the inclusion of N200 and P300 amplitudes and latencies to target stimuli. In order to satisfy the subject-to-variable ratio of DfA, only variables that produced significant results in the ANOVAs previously conducted were entered in the analysis. Independent DfAs were conducted for the chronic schizophrenia group versus their controls, and for the FESz group versus their controls. The variables included in the first DfA are listed in Table 5.4

Table 5.4 Variables entered for N100, P200 DfA.

<u>Chronic Sz</u>	<u>FESz</u>
T-1 N100 amplitude (Fz)	T-1 N100 amplitude (Fz)
T-1 P200 amplitude(Cz)	T-1 P200 amplitude(Cz)
T-1 P200 latency (Cz)	T-1 P200 latency (Cz)
target N100 amplitude (Fz)	target N100 amplitude (Fz)
target P200 latency (Cz)	target P200 latency (Cz)
T+1 N100 amplitude (Fz)	T+1 N100 amplitude (Fz)
T+1 P200 amplitude (Cz)	T+1 P200 amplitude (Cz)
T+1 P200 latency (Cz)	T+1 P200 latency (Cz)

Variables entered in the second DfA included target P300 amplitude and latency at Pz and N200 amplitude and latency at Fz (four variables).

#### 5.4.3 Topography effects

For topographical analysis, all left handers (chronic schizophrenia = 3 and FESz = 6) were removed from the data set. T- and T+1 ERP components, (N100 and P200) and target ERP measures (N100, P200, N200, P300 amplitude & latency) were submitted separately to a 4-way ANOVA (3-way for N200 and P300 as there was only the target condition) with the between-group factor of diagnosis (schizophrenic vs. controls) and the within-group factors of stimulus (*T-I*, target, *T+1*), hemisphere (left/right) and site (left = F3, F7, C3, T3, T5, P3; right = F4, F8, C4, T4, T6, P4). To examine anterior/posterior differences in topography a similar 2 Group X 3 Stimulus X 2 region (anterior/posterior) X 7 sites (anterior = Fp 1, Fp2, Fz, F3, F4, F7, F8; posterior = 15, T6, Pz, P3, P4, O1, O2), was conducted. Because the primary focus was on lateralisation and regional effects and their interaction with stimulus and group, only these results are reported. Differences among the site factor are partially described earlier and are not further elaborated here. The use of vector scaling of ERP data when performing topographical analysis recommended by Picton et al. (2000) was not employed because in this case it was not necessarily appropriate, as suggested by other researchers (Haig, Gordon, & Hook, 1997; Urbach & Kutas, 2002).

#### 5.4.4 Response time

Response times were determined for each participant to target tones. Only correct responses, defined as correctly identified targets for which a button press response was obtained within one second of the target tone, were analysed. The between-group (chronic schizophrenia vs. control, FESz vs control) differences were analysed by t-tests.

### 5.5 RESULTS

#### 5.5.1 Midline sites

The ERP waveforms are presented in Figures 5.1 and 5.2, the former to accentuate between-group differences at midline sites, and the latter to accentuate within group differences at the central site. Mean and standard deviation amplitude and latency scores appear in Table 5.5 and 5.6. A small percentage (between 1% and 2.5% in each group) of ERP measures were identified as outliers (greater or less than one and a half the interquartile range from the upper and lower quartile). All results below are based on data with outliers; however, results remained significant following removal of outliers and covarying for medication (CPZ equivalents). Non-significant results and values appear in Appendix 3 (the inclusion of these would make the results section unwieldy).

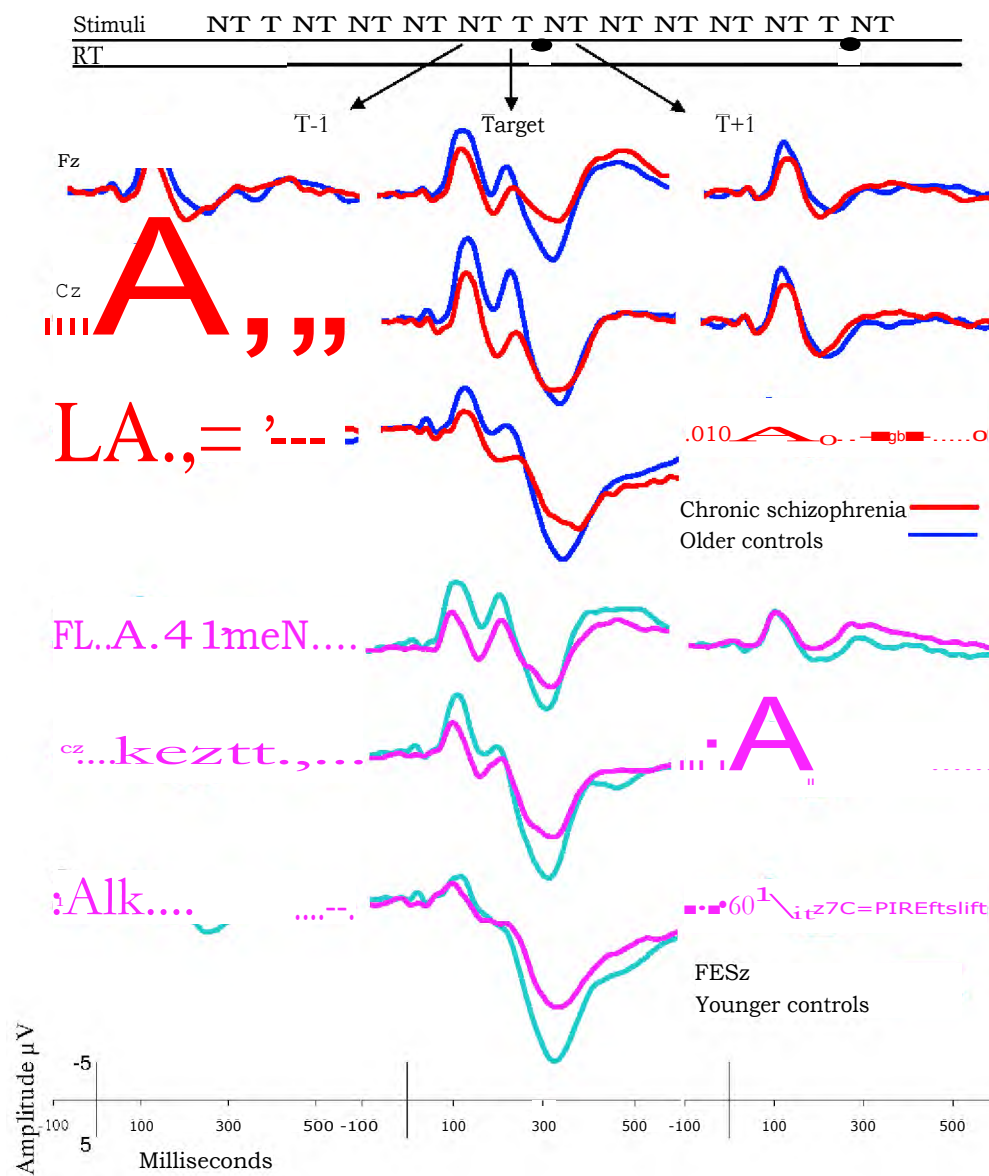


Figure 5.1 Average ERPs to target and non-target (T-1 & T+1) stimuli, at midline sites, superimposed to show between-group differences.



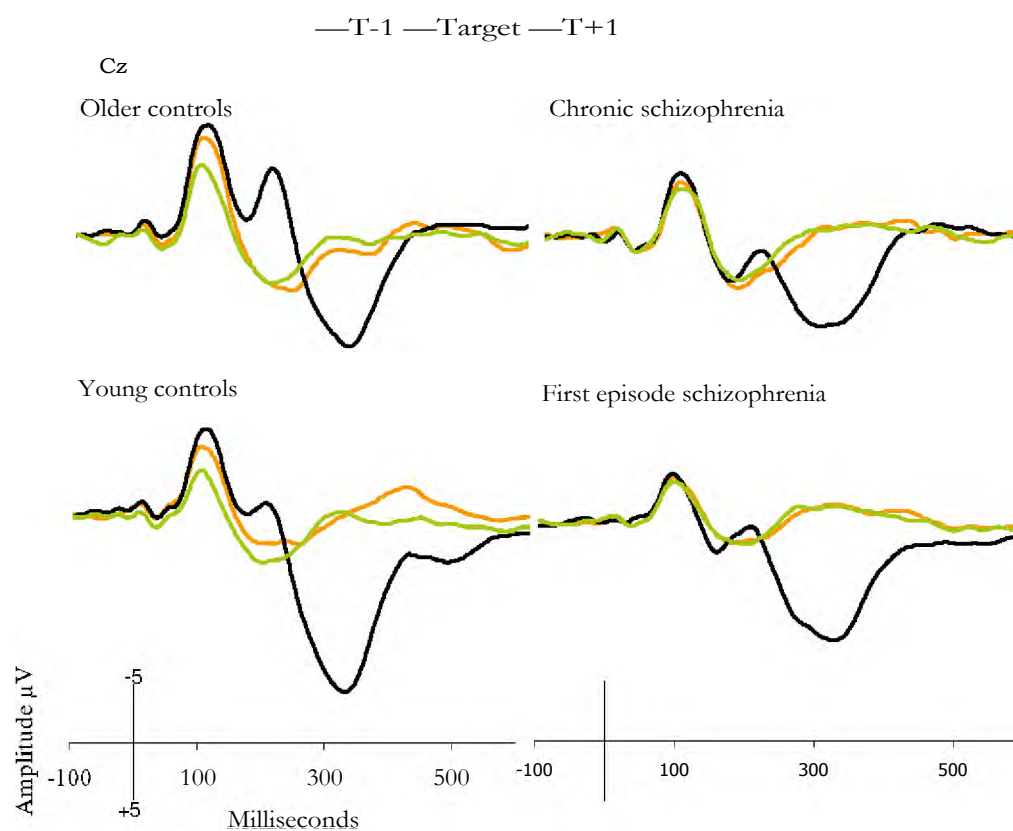


Figure 5.2 Average ERPs to target and non-target (T-1 & T+1) stimuli, superimposed to show within subject differences at Cz.

Table 5.5 N100 and P200 mean and SD values to target stimuli for clinical and control groups.

		Older NC		Chronic Sz		Yc	r NC	FESz	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
N100 amp	Fz	-9.1	2.6	-5.6	4.2	-7.5	4	-6.3	2.8
	Cz	-10.2	3.4	-5.9	3.5	-7.7	3.9	-5.5	2.8
	Pz	-6.2	2.7	-3.5	2.1	-5.2	2.7	-4	2.5
N100 lat	Fz	105.2	16.1	104.9	12.6	110.7	20.3	105.6	19.1
	Cz	103	11.4	104.5	11.2	106.1	16.6	101.5	18.1
	Pz	101.8	12.1	100.7	16.5	101.2	19	98.8	18.8
P200 amp	Fz	3.2	3.1	4.7	4.1	105	3.9	1.6	3.2
	Cz	5.8	2.9	6.1	3.2	4.6	4.6	3.8	3.4
	Pz	3.9	2.2	5.4	2.9	3.5	3.6	3.2	3
P200 lat	Fz	201.9	27.7	185.9	21.4	186.2	37.2	188.7	29.9
	Cz	203.7	26.4	182.6	19	184.2	31.2	192.8	28
	Pz	192.1	28.9	187.1	27.5	185.8	34.6	194.7	33
N100 amp	Fz	-10.2	3	-7.5	3.7	-10.6	4.1	-5.9	3.6
	Cz	-11.4	3.8	-7.1	3.6	-9.3	4.5	-5.4	3.4
	Pz	-6.6	3.1	4.2	2.4	-4.8	2.7	-3.9	3.1
N100 lat	Fz	108.3	16.6	106.6	14.9	110.4	16.7	106.5	15.8
	Cz	103.1	13.2	101.1	11	104.5	12.2	97.1	15
	Pz	101	12.6	98.7	12.9	96.2	11.5	94.3	19.4
P200 amp	Fz	0.8	3.7	3.5	4.6	-1.7	5.2	2.3	4.7
	Cz	-0.4	4.7	5.6	4.2	1.7	6.2	4	4.5
	Pz	1.5	3.3	5.4	3.1	3.5	5.8	4.5	3.8
P200 lat	Fz	172.4	16.1	178.5	15.3	171.9	17.3	168.4	13.9
	Cz	161.7	18.6	174.9	16.7	171.2	20.4	165.8	16.6
	Pz	163.2	17.4	178.5	21.3	160.8	31.7	158.1	25.2
N100 amp	Fz	-8.1	4.1	-6.2	4.5	-5.5	3.5	-5.6	3.5
	Cz	-7.5	3.6	-5.9	3.2	-5.4	3.8	-4.4	2.9
	Pz	-5.4	2.4	-4.3	2.5	-4.4	3.6	-3.5	3.1
N100 lat	Fz	100.5	12.7	105.7	16.8	106.9	17.5	113.5	31.7
	Cz	95.5	9.7	104	15.6	101.9	19.3	102.6	17.4
	Pz	98.6	13	101	19.2	100.7-1	16.4	95.2	18
P200 amp	Fz	3.4	4.3	3.9	3.6	3.3	3.9	1.8	4.1
	Cz	5.2	3.5	5.2	3.4	5.8	4.4	3	3.9
	Pz	3.7	3.2	3.5	2.7	4.1	3.4	2.2	3
P200 lat	Fz	199.7	26.4	182.3	20.6	185.4	20.3	181.6	25.5
	Cz	200.5	23.4	184.6	20	184.6	22.2	179.1	26.7
	Pz	199.5	26	181.1	21.9	184.6	23.2	172.2	31.7

Table 5.6 N200 and P300 Mean and SD to target stimuli for clinical and control groups.

		Older NC		Chronic Sz		Younger NC		FESz	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
N200 amp	Fz	-5.3	3.6	-3.9	4.4	-9.9	5.6	-5.8	4.6
	Cz	-7.5	5.9	-1.7	4.8	-3.2	7.2	-0.9	5.5
	Pz	-2.1	4.3	0.7	3.4	1.1	5.3	0.8	4.4
N200 lat	Fz	209.8	16.6	229.5	21.6	214.1	18.9	222.5	19.8
	Cz	207.2	13.1	220.6	18.2	209.3	18.1	216.1	21.6
	Pz	203.8	22.3	226.5	17.1	195.1	29.9	204.9	31
P300 amp	Fz	10.3	6.3	5.7	5.9	10.4	8.5	7.9	7.7
	Cz	11.9	8	11.2	7	18.9	10.6	13.3	8.2
	Pz	18.9	6.6	15.1	6.6	25.2	10.5	17.7	9.7
P300 lat	Fz	316.3	23.4	315.5	27.8	315.9	28.8	320.4	45.1
	Cz	316.8	23.7	309.2	32.6	316	35.8	317.7	38.5
	Pz	328	21.6	327.4	35.5	318.1	27.6	325.4	39.3

### 5.5.1.1 N100 Component

#### 5.5.1.1.1 *Amplitude*

N100 amplitude statistical results for chronic schizophrenia vs. older controls, and FESz v. younger controls are summarised in Table 5.7.

#### Chronic schizophrenia versus older controls

For N100 amplitude there was a significant main effect for group with the chronic schizophrenia group manifesting reduced N100 amplitude compared with older controls. This main effect for group was further qualified by Group X Stimulus, Group X Site and Group X Stimulus X Site interactions (see Table 5.7, values in blue & Figure 5.3) as follows. With regard to the target, non-target comparisons, significant group differences were observed at the central compared with the fronto-parietal sites indicating that the older control group had reduced N100 amplitude to non-target compared with target stimuli while the chronic schizophrenia group did not. Additionally, whereas the schizophrenia group did not differ in the way they responded to the two non-targets, controls did, with T+1 decreased compared with T-1, with this pattern being specific to the central site (see Table 5.7, values in blue & Figure 5.3).

Over group and site, targets produced larger amplitudes than non-targets, with this effect being pronounced at the central site rather than the fronto-parietal sites. The expected fronto-central maximum for N100 amplitude was also observed, with both linear and quadratic contrasts yielding significant results (see Table 5.7, values in green).

Contrasts			<i>Chronic Sz</i>		<i>FESz</i>	
<i>4f</i> (1,76)	Stimulus	Site				
Group			30.08	.0001	6.45	.01
Group X Stimulus	T vs NTs				9.61	.003
	T+1 vs T-1		6.14	.02		
Group X Site		Cz vs Fz & Pz	15.22	.0002	10.98	.001
		Fz vs Pz			3.93	.05
Group X Stim X Site	T vs NTs	Cz vs Fz & Pz	12.76	.0006	3.27	.07
		Fz vs Pz			31.32	.0001
	T+1 vs T-1	Cz vs Fz & Pz	11.44	.001		
		Fz vs Pz				
Stimulus	T vs NTs		15.78	.0002	15.37	.001
	Fz vs Pz				8.96	.004
Stimulus X Site	T vs NTs	Cz vs Fz & Pz	24.37	.0000	13.04	.001
		Fz vs Pz	9.84	.002	19.72	.001
	T+1 vs T-1	Cz vs Fz & Pz	37.2	0.0001	13.37	.001
		Fz vs Pz				
Site		Cz vs Fz & Pz	140.28	0.0001	25.86	.0001
		Fz vs Pz	123.65	0.0001	74.71	.0001
Gender			5.57	0.02	3.9	.05
Gender X Group						
Gen X Stim X Site	T vs NT	Cz vs Fz & Pz				
		Fz vs Pz				
	T+1 vs T-1	Cz vs Fz & Pz	8.57	0.005		
		Fz vs Pz				

Table 5.7 Summary of N100 amplitude results

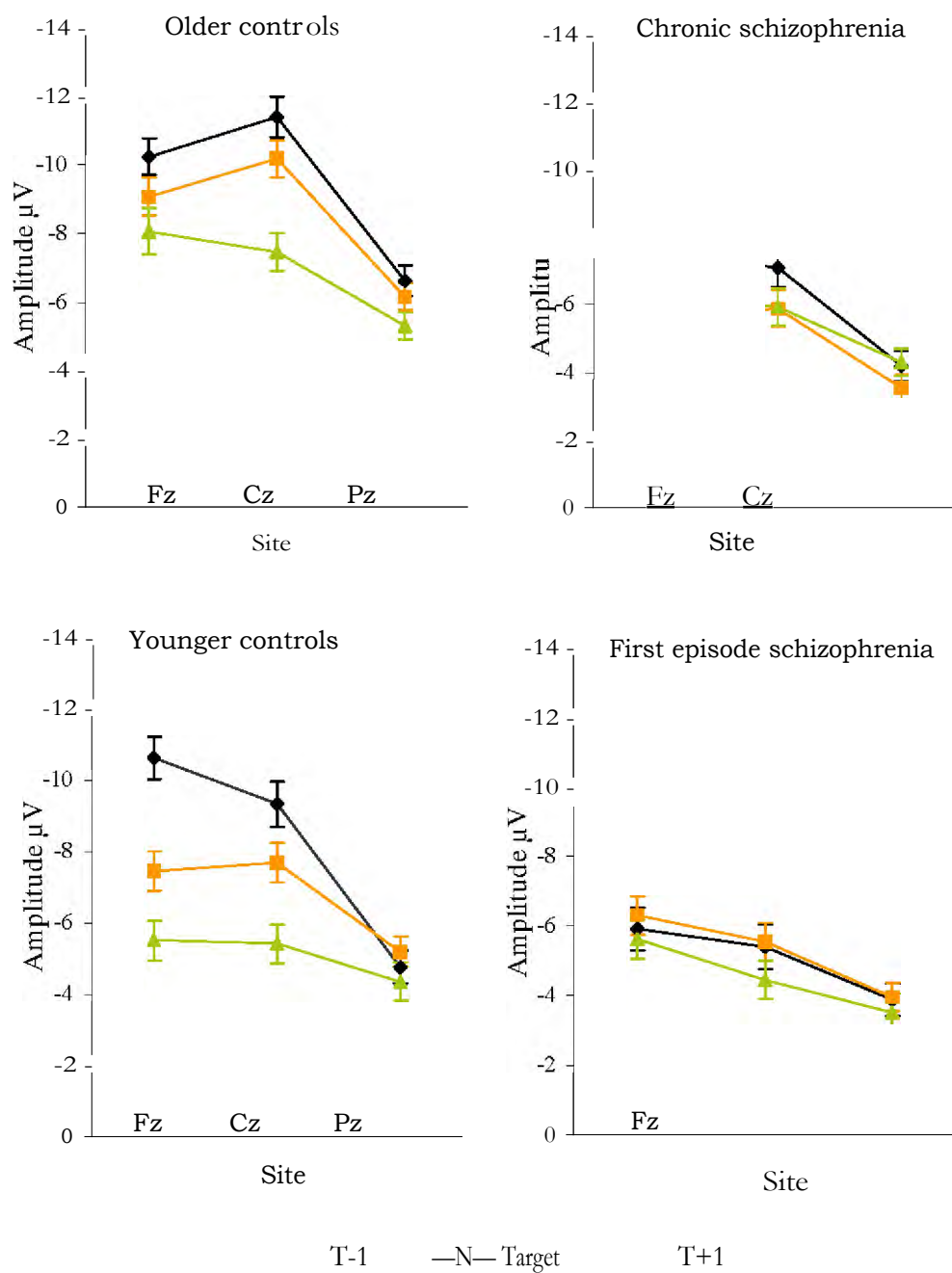


Figure 5.3 N100 amplitude to target and non-target stimulus at midline sites, for all groups.

The main effect for gender was significant (see Table 5.7, values in pink) with women producing larger amplitudes than men, with this effect further qualified by a Gender X Stimulus x Site interaction. In sum, the gender difference was maximal at frontal and parietal compared with the central site and greater for T+1 stimuli than for T-1 stimuli.

Summary: The chronic schizophrenia group did not differ in the way they responded to targets and non-targets however, the older controls did displaying larger N100s to targets compared to T-1, with this effect being prominent at the vertex.

#### FESz versus younger controls

There was a significant main effect for group, with the FESz group manifesting reduced N100 amplitude compared with younger controls. This main effect for group was further qualified by Group X Stimulus, Group X Site and Group X Stimulus X Site interactions, similar to those found in the chronic group (see Table 5.7, values in blue & Figure 5.3). With regard to the target versus non-target comparisons, significant group differences were observed at the fronto-central compared with the parietal site indicating the younger control group had reduced N100 amplitude to non-target compared with target stimuli, while the FESz group did not differ in their response to target and non-target stimuli.

Over group and site, targets produced larger amplitudes than non-targets, an effect more pronounced at the fronto-central, than parietal site (see Table 5.7, values in green). The expected fronto-central maximum for N100 amplitude was also

observed, with both linear and quadratic contrasts yielding significant results (see Table 5.7, values in red).

The main effect for gender was significant with women producing larger amplitudes than men. There no further interaction between gender and group, stimuli or site (see Table 5.7, values in pink).

Summary: The FESz group did not differ in the way they responded between targets and non-targets, however, the younger controls did displaying increased N100 to targets compared with non-targets, with this effect pronounced at the fronto-central rather than parietal sites.

#### *5.5.1.1.2 Latency*

Chronic schizophrenia versus older controls

Effects were not significant for group, or group interactions with stimuli or site. There was a significant quadratic comparison for Group X Site,  $F(1,76) = 5.27$ ,  $p < .05$  with earlier N100 latency for older controls compared with chronic schizophrenia, specific to the vertex.

There was a main effect for gender with earlier latencies for females compared to males,  $F(1,76) = 5.39$ ,  $p < .02$ . This effect was maximal in latencies to target compared with non-target stimuli,  $F(1,76) = 7.46$ ,  $p < .01$ , at central cf, frontal and parietal sites,  $F(1,76) = 4.05$ ,  $p < .05$ . For the non-target contrast, females



showed earlier latencies to T-1 compared with T+1 stimulus, with this effect maximal at frontal compared with parietal sites.  $F(1,76) = 4.96, p < .05$ .

FESz vs. younger controls

Effects were not significant for group or group interactions with stimuli or site for N100 latency. Nor were effects for gender significant as a main effect, or as an interaction with group stimulus or site.

#### 5.5.1.1.3 Relationship between N100 and age

Non-tar.Qets: N100 amplitude increased with age for non-target, *T-I*, and *T+I*, stimuli at the central site for the younger control group, but not for the schizophrenia group (see Table 5.8). Correlations between non-target N100 latency and age were not significant.

Table 5.8 Pearsons two-tailed correlations between age and N100 amplitude<sup>2</sup>

	Non-target		Target
	T-1	T+1	
Control	$r = -.34, p < .002$	$r = -.24, p < .05$	$r = -.29, p = .01$
Schizophrenia			$r = -.34, p < .01$

Targets: N100 amplitude increased with age for target stimuli, at the central site for both the control and schizophrenia groups. However, further analysis revealed that

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Note that as N100 is a negative component. Hence correlations with N100 amplitude are the inverse of the *r* value sign.

these results were influenced by illness duration rather than age, because the correlation for the schizophrenia group did not remain significant after controlling for the effects of duration,  $r = -.2$ ,  $p = .09$ , or the combination of duration and medication,  $r = -.1$ ,  $p = .59$ . Correlations between target N100 latency and age were not significant.

#### 5.5.1.1.4 Relationship between N100 and symptomatology

N100 amplitude correlated with the disorganisation factor at the central site across stimuli in the chronic schizophrenia group, and in the FESz group for non-target but not target stimuli, indicating that the higher the score on the disorganisation factor the more reduced the N100 amplitude<sup>3</sup> ( see Table 5.8). N100 latency did not correlate with symptom factors.

Table 5.9 N100 amplitude 2-tailed Pearson correlations with Disorganisation factor.

	Chronic schizophrenia	FESz
<i>T-1</i>	$r = .42, p = .01$	$r = .41, p = .02$
Target	$r = .35, p = .03$	—————
<i>T+1</i>	$r = .36, p = .03$	$r = .33, p = .06$

#### 5.5.1.1.5 Summary

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<sup>3</sup> Note that as N100 is a negative component. Hence correlations with N100 amplitude are the inverse of the  $r$  value sign.

Both chronic and FESz groups showed reduced N100 amplitude overall compared with controls, with the reduction to target stimuli mainly contributing to this result. Neither clinical group, showed the differential response between target and non-target stimuli, reduced N100 amplitude to non-target compared with target stimuli that was found in the control group. The chronic schizophrenia group did not show the differentiation between non-target stimuli, reduced N100 amplitude to T+1 compared with T-1, displayed by the older control group. Reduced N100 amplitude was found for males compared with females, across control and clinical groups. However the enhanced N100 amplitudes associated with age, for non-target stimuli was found in the control groups, but not in the clinical groups. Higher disorganisation scores were related with reduced N100 amplitude across stimuli, but maximally with non-target stimuli.

#### 5.5.1.2 P200 Component

##### *5.5.1.2.1 Amplitude*

The results of the statistical analyses are summarised in Table 5.10.

#### Chronic schizophrenia versus older controls

There was a significant main effect for group, with the chronic schizophrenia group demonstrating increased P200 amplitude compared with older controls. This main effect was qualified by significant Group X Stimulus, Group X Site and Group X Stimulus X Site interactions as described below (see Table 5.10, values in blue & Figure 5.4). With regard to the target vs. non-target comparisons, whereas the chronic schizophrenia group responded similarly to target and non-target stimuli, older

controls responded differentially, with decreased P200 to target compared with non-target stimuli, with this difference being most marked at the vertex (see Figure 5.4).

Table 5.10 Summary of results for P200 amplitude

<i>Contrasts</i>			Chronic Sz		FESz	
	Stimulus	Site	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
4f (1,76)						
Group			12.21	.001	--	
Group X Stimulus	T vs NTs		24.98	.000	5.45	.022
	T-1 vs T+1			--	3.90	.052
Group X Site		Cz vs Fz & Pz	3.62	.061		
		Fz vs Pz		--	4.36	.040
Group X Stim X Site	T vs NTs	Cz vs Fz & Pz	18.87	.000		
		Fz vs Pz	3.60	.062	3.98	.050
	T-1 vs T+1	Cz vs Fz & Pz				
		Fz vs Pz				
Stimulus	T vs NTs		12.35	.001		
	T-1 vs T+1					
Stimulus X Site	T vs NTs	Cz vs Fz & Pz	25.17	.000	3.81	.05
		Fz vs Pz	7.54	.008	12.78	.001
	T-1 vs T+1	Cz vs Fz & Pz	3.62	.061		
		Fz vs Pz		--	5.51	.02
Site		Cz vs Fz & Pz	57.16	.000	47.79	.000
		Fz vs Pz	4.11	.046	33.63	.000
Gender						
Gender X Group						
Gender X Stimulus	T vs NTs		8.83	.004		
	T-1 vs T+1					
Gender X Site		Cz vs Fz & Pz				
		Fz vs Pz	3.54	0.064		
Gen X Stim X Site	T vs NTs	Cz vs Fz & Pz	4.73	.033		
		Fz vs Pz				
	T-1 vs T+1	Cz vs Fz & Pz	8.32	.005		
		Fz vs Pz				

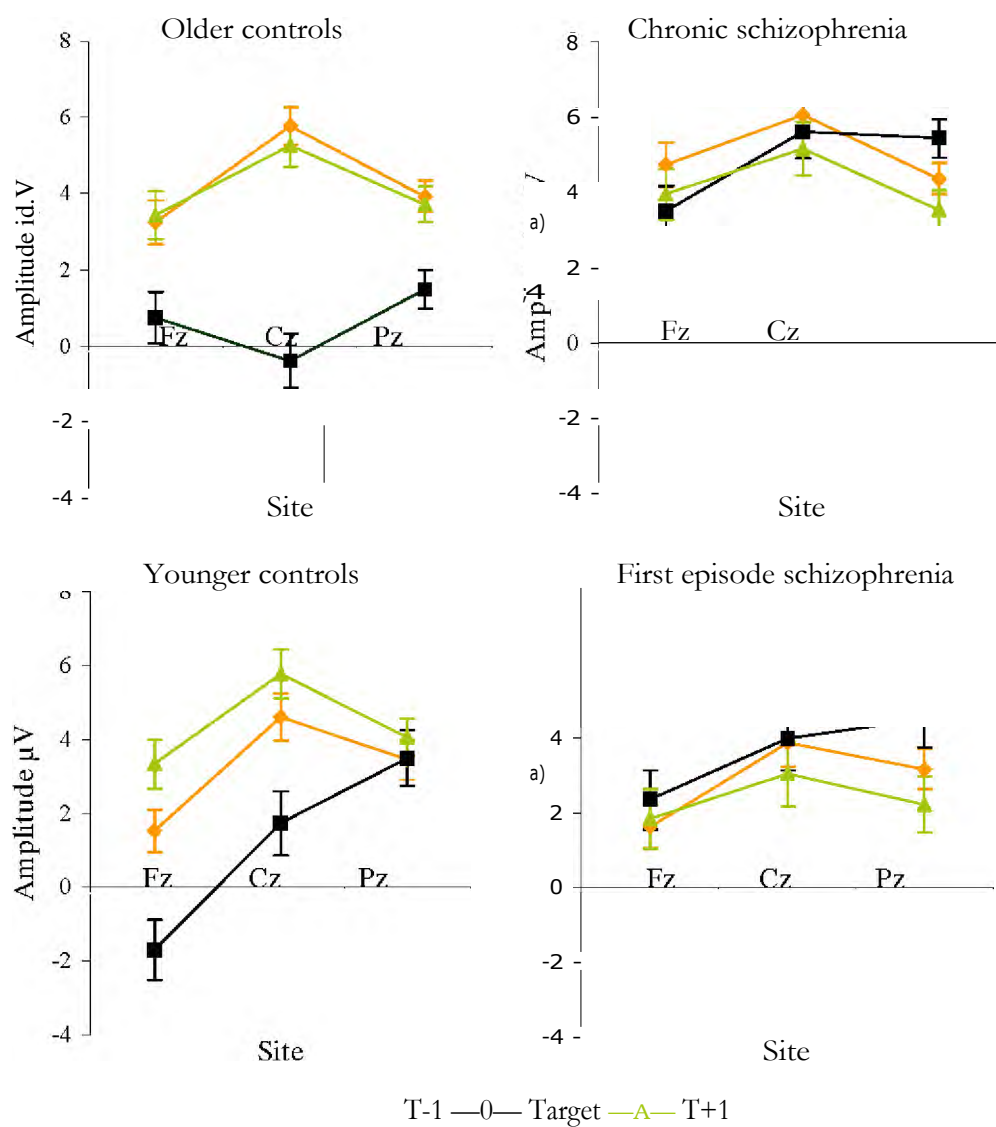


Figure 5.4 P200 amplitude to target and non-target stimulus at midline sites, for all groups.

Over group and site, targets produced reduced amplitudes compared with non-targets, with this effect being most pronounced at the central site. As mentioned above, this effect was qualified by a group interaction with the results of the older control group contributing to these effects (see Table 5.10 values in green). Additionally across group P200 amplitude appeared to be reduced to T+1 compared with T-1, at the central compared with frontal and parietal sites, with the results approaching significance ( $p = .06$ ). The expected centro-parital maximum for P200 amplitude was also observed, with both linear and quadratic contrasts yielding significant results (see Table 5.10, values in red).

Although effects were not significant for gender or Gender X Group, there were significant Gender X Stimulus and Gender X Stimulus X Site interactions as follow (see Table 5.10, values in pink). Across groups, males demonstrated reduced P200 amplitude to targets compared with non-target stimulus and to T-1 compared with T+1 stimulus, with this effect maximal at the central compared with frontal and parietal sites.

#### FESz versus younger controls

The main effect for group was not significant. However, there were significant Group X Stimulus, Group X Site, and Group X Stimulus X Site interactions for P200 amplitude as follows (see Table 5.10, values in blue and Figure 5.4). The FESz group responded similarly to target and non-target stimuli, whereas younger controls responded differentially with decreased P200 to target compared with non-target stimuli, with the difference being most marked at Fz (see Figure 5.4).

Additionally, whereas the FESz group did not differ in the way they responded to the two non-targets, younger controls did, showing T-1 decreased compared with T+1. As a result the FESz group demonstrated increased P200 to target stimulus compared with younger controls and decreased P200 to T+1 stimulus compared with younger controls (see Figure 5.4).

Over group P200 amplitude to target stimuli was reduced compared with non-target stimuli, with this effect maximal at fronto-central compared with parietal sites, and P200 amplitude was reduced to T-1 compared with T+1 stimuli at frontal compared with parietal sites. As mentioned above, these effects were qualified by group interaction with the results of the younger control group contributing to these effects.

Significant linear and quadratic effects indicated that amplitude was maximal centro-parietally over group and stimuli. Effects were not significant for gender or interactions between gender and other factors such as group, stimulus or site.

#### *5.5.1.2.2 Latency*

The results of the statistical analyses are summarised in Table 5.11.

Chronic schizophrenia versus older controls

For P200 latency, there was a significant main effect for group, with the chronic schizophrenia group manifesting earlier P200 latency compared with older controls. This main effect for group was further qualified by Group X Stimulus and Group X Stimulus X Site interactions as described below. With regard to the target

vs. non-target comparisons, whereas the chronic schizophrenia group responded similarly to target and non-target stimuli, older controls responded differentially, with dramatically earlier P200 to target compared with non-target stimuli, the difference being most marked at Cz (see Table 5.11, values in blue & Figure 5.5). Thus, the finding of earlier latency in the chronic schizophrenia group compared with older controls was specific to non-target stimuli, with P200 latency to target stimuli prolonged in the chronic schizophrenia group compared with older controls (see Figure 5.5).

Over group and site, targets produced earlier latencies than non-targets, with this effect being maximal at the central site (see Table 5.10, values in green). As mentioned earlier, this stimulus effect was more dramatic for the older control group. There was also a main effect for site with P200 most prolonged at parietal compared with frontal sites (see Table 5.10, values in red).

Although effects were not significant for gender or Gender X Group, there were significant Gender X Group X Stimuli, Gender X Group X Site and Gender X Group X Stimuli X Site interactions as follow (see Table 5.10, values in pink & Figure 5.6). Essentially the pattern identified above, whereby the chronic schizophrenia group responded more uniformly to both targets and non-targets, was replicated for both males and females, with the between-group differences (schizophrenia vs. older control) being more marked for females than they were for males. The four-way interaction involving the site factor suggested that parietal site



was more sensitive to between-group differences for females, while the central site was more sensitive for males.

Table 5.11 Summary of P200 latency results

4f(1,76)	<i>Contrasts</i>		Chronic Sz		FESz	
Factor	Stimulus	Site	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Group			5.62	.02	--	
Group X Stimulus	T vs NTs		40.50	.0000	3.72	.06
	T-1 vs T+1					
Group X Site		Cz vs Fz & Pz				
		Fz vs Pz				
Group X Stim X Site	T vs NTs	Cz vs Fz & Pz	3.88	0.05	--	
		Fz vs Pz				
	T-1 vs T+1	Cz vs Fz & Pz				
		Fz vs Pz				
Stimulus	T vs NTs		65.18	.0001	32.95	.0001
	T-1 vs T+1					
Stimulus X Site	T vs NTs	Cz vs Fz & Pz	15.51	0.0002	--	
		Fz vs Pz			4.30	.04
	T-1 vs T+1	Cz vs Fz & Pz				
		Fz vs Pz	3.43	.07	--	
Site		Cz vs Fz & Pz	--			
		Fz vs Pz	4.37	.04	--	
Gender						
Gender X Group						
Gen X Group X Stim	T vs NTs		4.67	.03	--	
	T-1 vs T+1					
Gen X Group X Site		Cz vs Fz & Pz	3.64	.06	--	
		Fz vs Pz	4.32	.04	--	
Gen X Group X Stimuli X Site	T vs NTs	Cz vs Fz & Pz	5.54	.02	5.22	.02
		Fz vs Pz				
	T-1 vs T+1	Cz vs Fz & Pz				
		Fz vs Pz				

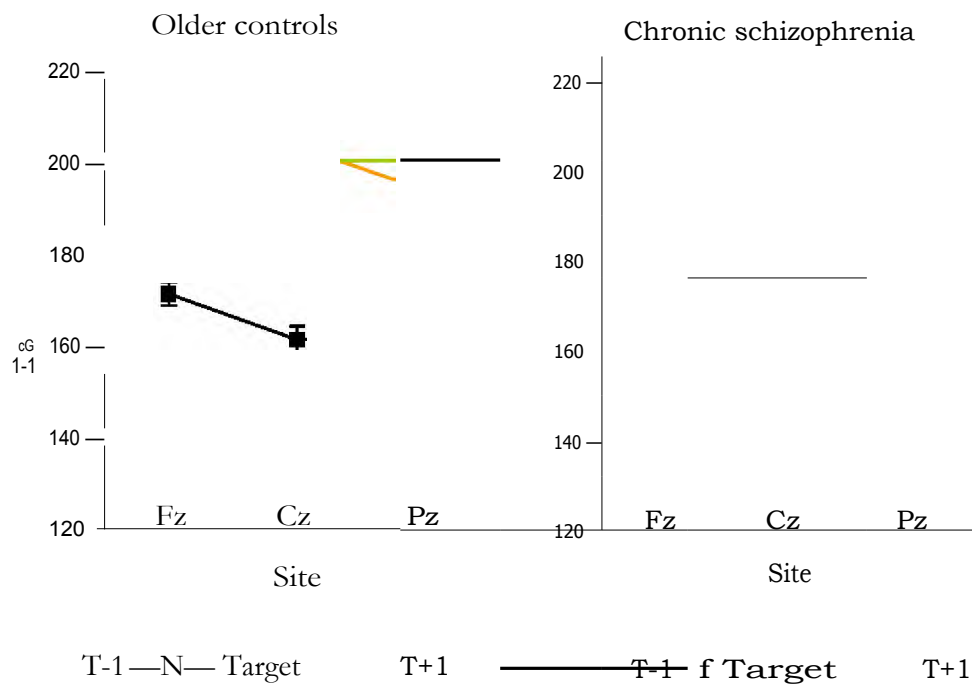


Figure 5.5 P200 latency to target and non-target stimuli at midline sites for chronic schizophrenia and older controls

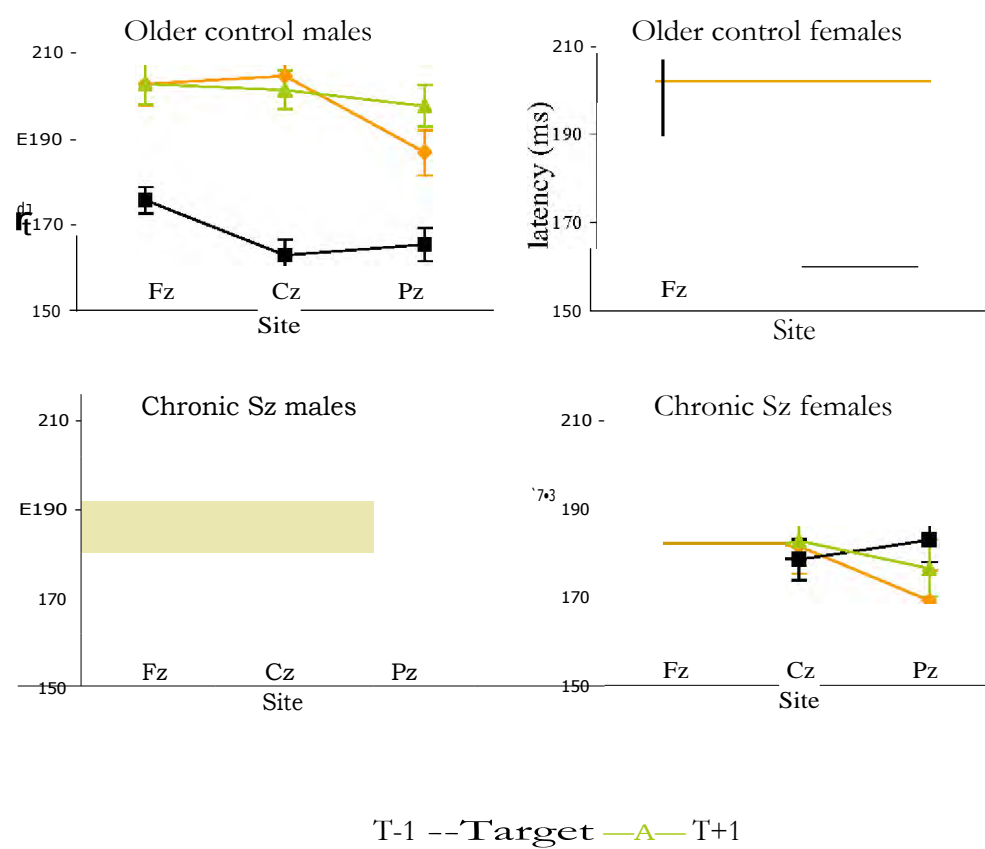


Figure 5.6 P200 latency to target and non-target stimulus in males and females, for chronic schizophrenia and older control groups

## FESz versus younger controls

Effects were not significant for Group, Group X Stimulus, Group X Site or Group X Stimulus X Site for P200 latency. Over group and site, targets were responded to earlier than non-targets, with this effect maximal parietally (see Table 5.10, values in green). There was a significant Gender X Group X Stimulus X Site interaction (see Table 5.10, values in pink, Figure 5.7) indicating that males responded earlier to targets compared with non-targets, (see Table 5.10, values in pink, Figure 5.7), whereas females responded similarly to target and non-target stimulus across both group. Quadratic contrasts indicated that this effect was maximal at central compared with frontal or parietal sites.

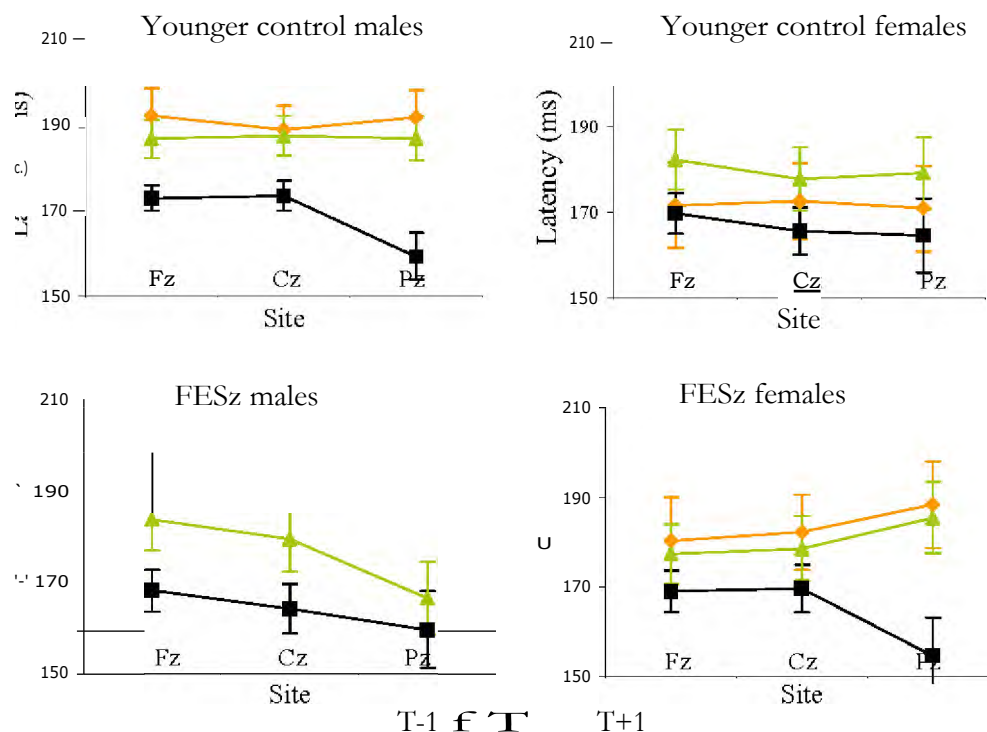


Figure 5.7 P200 latency to target and non-target stimulus in males and females, for FESz and younger control groups.

#### *5.5.1.2.3 Relationship between P200 and age*

*Non-targets:* Correlations between age and P200 amplitude to non-target stimuli at the central site were not significant in the control group however there was a positive correlation between age and P200 amplitude to T+1 stimuli,  $r = .24$ ,  $p < .05$ , for the schizophrenia group. In the control group P200 latency to T-1 and T+1 was delayed with age progression,  $r = .27$ ,  $p < .02$  and T+1,  $r = .32$ ,  $p < .01$ , respectively, while age and latency to non-target stimuli were not significantly correlated in the schizophrenia group.

*Targets:* Correlations between target P200 amplitude and age were not significant for the control or schizophrenia group. For P200 latency, the schizophrenia group showed a significant correlation between age and P200 latency to target stimuli,  $r = .23$ ,  $p < .05$  with latency increasing with age.

#### *5.5.1.2.4 Relationship between P200 and symptomatology*

Correlations between symptom factors and P200 amplitude and latency were not significant.

#### *5.5.1.2.5 Summary*

Both control groups had earlier and reduced P200 components to targets and delayed and increased to non-target stimuli. This differentiation was not found in the chronic schizophrenia group. The FESz group differentiated between target and non-target stimuli in latency, but not in amplitude. The combined schizophrenia group did

not show prolonged P200 latency to non-target stimuli with age as the combined control group did. Differential gender effects were found for both amplitude (present in clinical not in control groups) and latency (present in control but not in clinical groups).

### 5.5.1.3 N200

#### 5.5.1.3.1 Amplitude

Chronic schizophrenia versus older controls

There was a significant main effect for group,  $F(1,78) = 17.98$ ,  $p < .001$ , with N200 reduced in the chronic schizophrenia group compared with the older control group. This was qualified by a significant Group X Site interaction with the quadratic contrast,  $F(1,76) = 19.8$ ,  $p < .0001$ , indicating that the group difference was maximal at Cz (see Figure 5.8). Significant quadratic,  $F(1,76) = 10.73$ ,  $p < .001$ , and linear,  $F(1,76) = 132.9$ ,  $p < .0001$ , contrasts for site indicated N200 was maximal at fronto-central sites.

There was also a significant main effect for gender,  $F(1,76) = 7.6$ ,  $p < .01$ , with N200 reduced in females compared to males, and a significant Gender X Group X Site linear contrast,  $F(1,76) = 4.39$ ,  $p < .05$ , as the reduced N200 for the chronic group was due to difference between female rather than male subjects, with this effect specific to the frontal site.

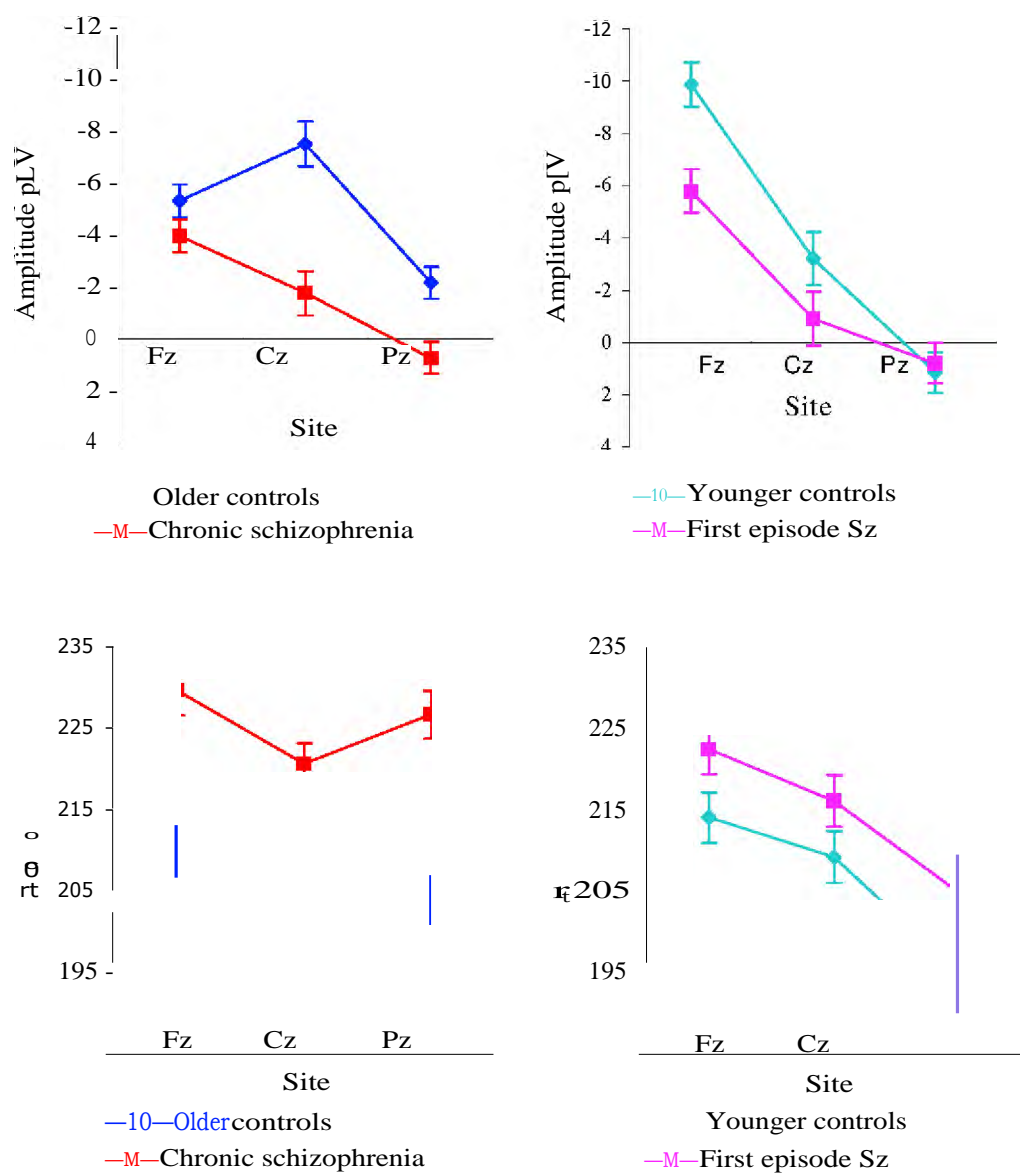


Figure 5.8 N200 amplitude (above) and latency (below) at midline sites for clinical and control groups.

FESz versus younger controls

The main effect for group was not significant, however, there was a significant Group X Site linear contrast,  $F(1, 75) = 6.76$ ,  $p < .01$ , as the first episode group demonstrated reduced P200 amplitude at the frontal compared with the parietal site. There were significant linear,  $F(1,75) = 132.95$ ,  $p < .001$ , and quadratic,  $F(1,75) = 10.73$ ,  $p < .01$ , contrasts for site indicating a fronto-central maximum for N200 amplitude. Effects for gender were not significant, nor were any interaction effects for gender with group or site significant.

#### 5.5.1.3.2 Latency

Chronic schizophrenia versus older control

There was a significant main effect for group,  $F(1,76) = 5.25$ ,  $p < .05$ , with N200 latency prolonged in the chronic schizophrenia group compared with older controls. This main effect was qualified by a Group X Site interaction with the significant quadratic contrast,  $F(1,76) = 11.89$ ,  $p < .001$ , indicating this delay was maximal at frontal and parietal sites compared with the central site (see Figure 5.8). Significant linear,  $F(1,76) = 152.75$ ,  $p < .0001$  and quadratic,  $F(1,76) = 4.52$ ,  $p < .05$ , contrasts for site indicated that latency was maximal frontally, plateauing at central and parietal sites.

Effects for gender were not significant, nor were any interaction effects for gender with group or site significant.



#### FESz versus younger controls

Main effects for group were not significant. Across groups there was a significant linear contrast,  $F(1,75) = 24.20$ ,  $p < .0001$ , for site with N200 latency prolonged at frontal compared with central and parietal sites. Site and Group did not interact significantly.

Effects for gender were not significant, nor were any interaction effects for gender with group or site significant.

##### *5.5.1.3.3 Relationship between A1200 and age*

N200 amplitude to target stimulus decreased with age for the combined control group,  $r = .439$ ,  $p < .05$ , but not for the combined schizophrenia group,  $r = .21$ ,  $p = .07$ . Correlations between target N200 latency and age were not significant for the combined control or combined schizophrenia group.

##### *5.5.1.3.4 Relationship between the A1200 and symptomatology*

Correlations between N200 amplitude and latency at Fz and symptom factors were not significant.

##### *5.5.1.3.5 Summary*

A significant reduced and prolonged N200 occurred in chronic schizophrenia and a similar trend occurred in the FESz group (latency was significant when extended over full topography [see topographical analysis 5.2.2], while not

significant over midline sites). The reduction was maximal centrally in the chronic group and frontally in the first episode group. The decrease in N200 amplitude with age progression found in the combined control group did not reach significance in the schizophrenia group. No gender effects or correlations with symptom factors were found.

#### 5.5.1.4 P300 Component

#### 5.5.1.5 Amplitude

##### Chronic schizophrenia versus older controls

The chronic schizophrenia group showed an overall reduced P300 amplitude,  $F(1,76) = 5.25, p < .05$ . This main effect was qualified by a Group X Site interaction with the significant quadratic contrast,  $F(1,76) = 11.89, p < .001$  indicating this reduction was maximal at frontal and parietal sites compared with the central site (see Figure 5.9). There was also a main effect for site, with linear,  $F(1,78) = 161.39, p < .001$  and quadratic,  $F(1,78) = 4.30, p < .05$ , contrasts indicating maximal amplitude at the parietal site, plateauing between fronto-central sites (see Figure 5.9). Neither the main effect for gender, nor any of its interaction effects were significant.

##### FESz versus younger controls

There was a significant main effect for group,  $F(1,78) = 5.31, p < .05$  with the FESz group manifesting reduced P300 amplitude compared with younger controls. This main effect for group was further qualified by a Group X Site interaction, with a significant linear contrast,  $F(1,78) = 4.34, p < .05$ , indicating that

this reduction was maximal at the parietal compared with the frontal site (see Figure 5.9). There was also a significant linear contrast for site, with P300 amplitude maximal at the parietal site. Effects for gender were not significant, nor were any interaction effects for gender with group or site significant.

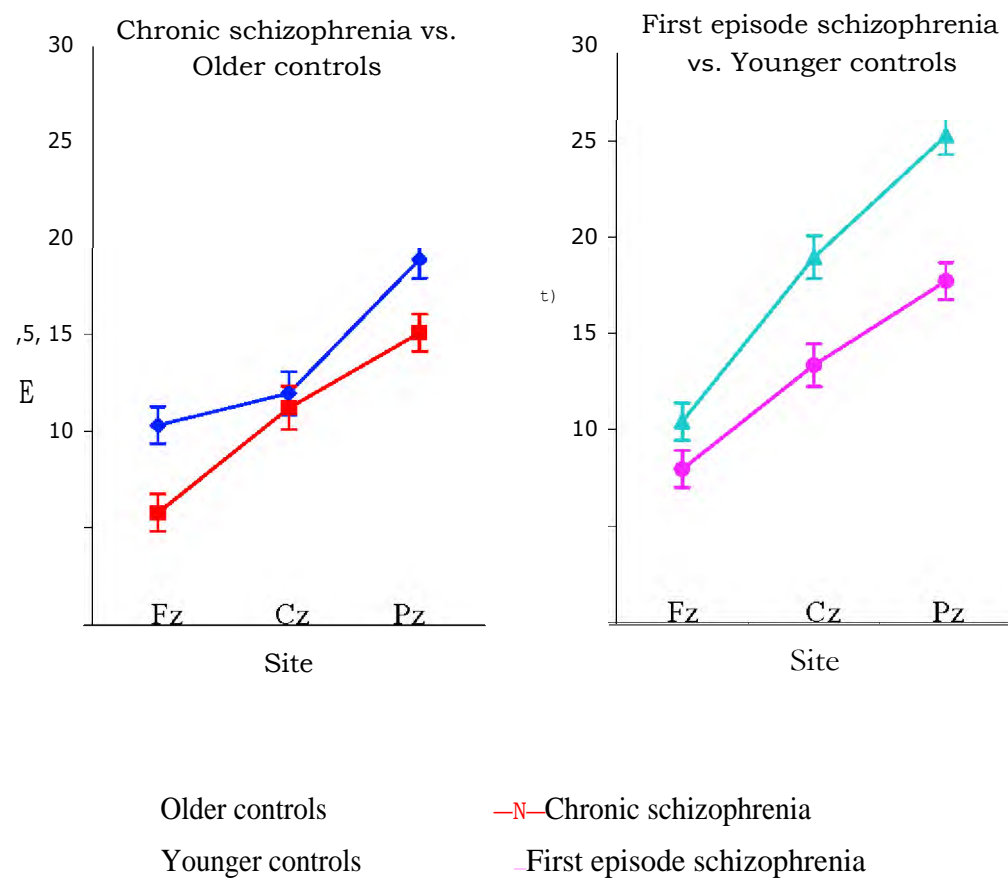


Figure 5.9 P300 amplitude at midline sites.

#### 5.5.1.5.1 Latency

##### Chronic schizophrenia versus older controls

Main effects for group were not significant. Across groups, there were significant linear,  $F(1,76) = 10.15$ ,  $p < .01$ , and quadratic,  $F(1,76) = 14.71$ ,  $p < .001$ , contrasts for site, with P300 latency prolonged maximally at the parietal site (See mean values in Table 5.6). Site and Group did not interact significantly. Effects for gender were not significant, nor were any interaction effects for gender with group or site significant.

##### FESz versus younger controls

For P300 latency there was no significant effects for group, site, group by site interaction, or gender.

#### 5.5.1.5.2 Relationship between P300 and age

P300 amplitude to target stimulus decreased with increases in age for both the control group,  $r = -.39$ ,  $p < .001$ , and the schizophrenia group,  $r = -.22$ ,  $p = .05$ . Although this relationship was stronger for the controls group, a Z test comparison did not reveal a significant difference between these two correlations,  $z_{dill} = -1.19$ ,  $p = 0.23$ . When the effects of duration of illness were taken in to account, the correlation between age and P300 amplitude in schizophrenia did not remain significant,  $r = -.12$ ,  $p = .32$ . This analysis was also applied to the chronic schizophrenia group alone, as the first episode group where assessed at onset. In this analysis, again the relationship between P300 amplitude and age was no longer significant when the correlation controlled for duration,  $r = -.04$ ,  $p = .80$ .

Increasing age has consistently been found to be associated with prolonged P300 latency, and this prediction was supported in the current Study with P300 latency being positively correlated with age,  $r = .205$ ,  $p = .03$  (one-tailed test) in the combined control group, but not in the combined schizophrenia group,  $r = -.12$ ,  $p = .432$  (one-tailed test).

#### *5.5.1.5.3 Relationship between P300 and symptomatology*

There were no significant correlations between P300 amplitude or latency and the symptom factors.

#### *5.5.1.5.4 Summary*

P300 amplitude was reduced for both the chronic and FESz groups compared with normal controls. P300 amplitude was observed to reduce with age for both the normal and schizophrenia groups. However the P300 reduction in the schizophrenia group was related more to illness duration than age. P300 latency was prolonged with age in the combined control group but not in the combined schizophrenia group. There were no gender effects or symptom correlations for P300 amplitude or latency.

### 5.5.1.6 Discriminant Function Analysis

To compare the relative accuracy of classification, schizophrenia or normal, based on target and non-target N100, P200 components compared with target N200, P300 components this Study compared two separate stepwise discriminant function analyses. The results of these analyses are summarised in Table 5.12, showing improved classification from the DfA based on the earlier N100 and 200 components to target and non-target stimuli compared with the DfA based on N200 and P300 to targets.

Table 5.12 Discriminant function analysis classification results

	Chronic schizophrenia	Older control	FESz	Younger control
1. N100 P200	82.5%	82.5%	82.5%	80%
	Wilk's 2(2,76) = 0.69, $\chi^2 = 28.5, p = .000$		Wilk's 2(3,78) = 0.56, $Z = 44.81, p = .000$	
Variables selected by stepwise DA (standardized canonical discriminant function)	T P200 latency (0.62) T-1 P200 latency (-0.49) T-1 N100 amplitude (0.49)		T N100 amplitude (1.06) T+1 N100 amplitude (-0.46)	
2. N200 P300	75%	65%	62.5%	77.5%
	Wilk's 42,77) = 0.82, $\chi^2 = 15.78, p = .000$		Wilk's 41,78) = 0.79, $\chi^2 = 18.49, p = .000$	
Variables selected by stepwise DA (standardized canonical discriminant function)	N200 latency (1.0)		P300 amplitude (0.72) N200 amplitude (-0.62)	

### 5.5.2 Topography

The effects of factors, including group and stimulus, along with their interactions, have been examined earlier for midline sites. Hence the following analyses focuses on main and interaction effects associated with hemisphere (left vs. right) and region (anterior vs. posterior). Results for other factors including group and stimulus emerging from this analysis replicate results from the earlier analysis and will not be reported here, but details are made available in a CD Rom in Appendix 3. Also only statistical values at .05 or above are reported below, with more comprehensive outputs available in Appendix 3.

#### 5.5.2.1 N100 component

##### *5.5.2.1.1 Amplitude*

Topographical head maps for N100 amplitude to target and non-target stimuli, for control and clinical groups appear in Figure 5.10. The results of the statistical analysis are summarised in Table 5.13.

Figure 5.10 N100 amplitude topographical head maps for target and non-target stimulus for clinical and control groups.



Table 5.13 Summary of N100 amplitude results

			<i>Chronic Sz</i>	<i>FESz</i>
	Stimulus	Location	<i>F</i>	
Hemisphere		L vs R		
Hemisphere Group		L vs R		
Hemisphere X Stim	T vs NTs	L vs R		
	T-1 vs T+1	L vs R	10.51 .002	--
Hem X Grp X Stim	T vs NTs	L vs R		
	T-1 vs T+1	L vs R		
Region		A vs P	97.06 .000	100.75 .000
Region X Group		A vs P		5.11 .027
Region X Stim	T vs NTs	A vs P	7.18 .009	28.45 .000
	T-1 vs T+1	A vs P		
Region X Grp X Stim	T vs NTs	A vs P		19.61 .000
	T-1 vs T+1	A vs P		

## Chronic schizophrenia versus Older controls

## Left versus right hemisphere

Neither the main effect for hemisphere nor its interaction with group was significant. However, the Hemisphere X Stimulus interaction for the T+1 vs. T-1 contrast was significant indicating increased N100 amplitude to T-1 compared with T+1 in the left compared with the right hemisphere, (see Table 5.13 values in blue & Figure 5.11).

## Anterior versus posterior

There was a significant effect for region signifying increased N100 amplitude in the anterior compared with the posterior region and a significant Region X Stimulus interaction, with the increase in N100 amplitude to target compared with non-target stimulus maximal in the anterior region (see Table 5.13 values in green & Figure 5.11).

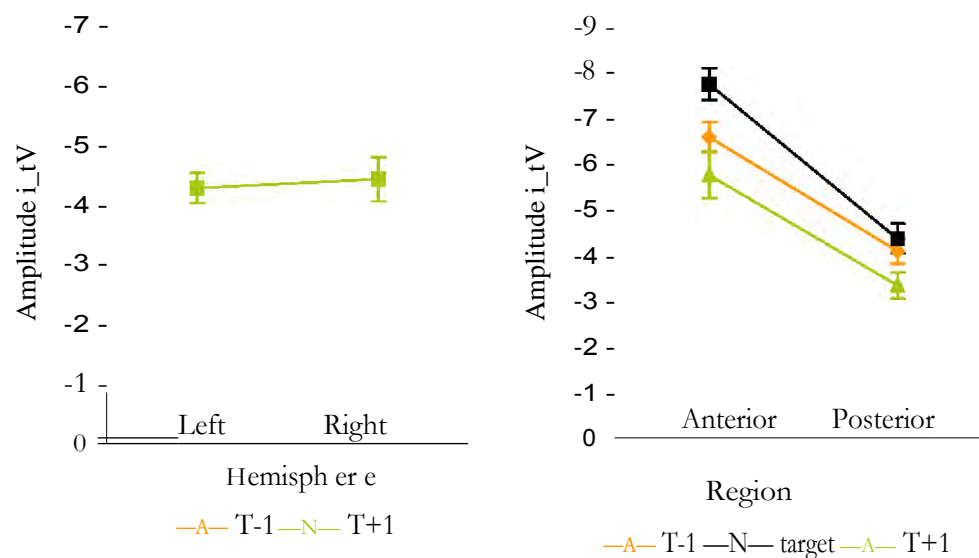


Figure 5.11 N100 amplitude to non-target stimuli by hemisphere (left panel) and to target and non-target stimuli by region (right panel), across chronic schizophrenia and older control groups.

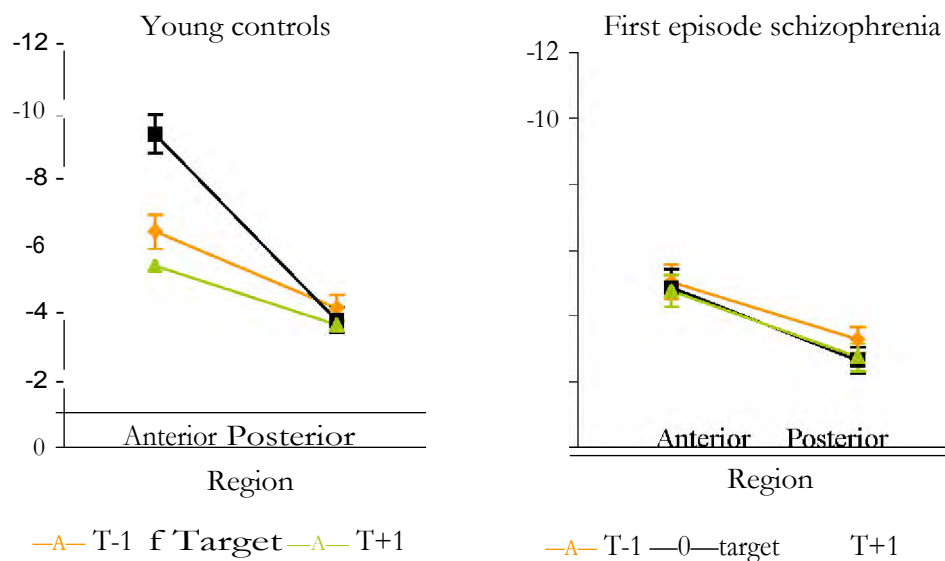


Figure 5.12 N100 amplitude by region in FESz and younger controls.

FESz versus Younger controls.

Left versus right hemisphere

Neither the main effect for hemisphere nor any of its interaction effects were significant (see Table 5.13 values in blue).

Anterior versus posterior

The main effect for region was significant indicating that, N100 amplitude increased in the anterior compared with the posterior region. This effect was qualified, however, by Region X Group, Region X Stimulus and Group X Region X Stimulus interactions. The critical finding was that the younger control group responded with increased N100 amplitude to target (compared with non-target) stimuli, where as the FESz group did not, with this group difference being observable only in the anterior region (see Table 5.13, values in green & Figure 5.12).

Summary

Over the older control and chronic schizophrenia groups, differences between T-1 and T+1 were more obvious in recordings over left (vs. right) hemisphere, as N100amplitude to T-1, but not T+1, was increased in the left (vs right) hemisphere. An increase in N100 amplitude to target compared with non-target stimuli found across the older control and chronic schizophrenia groups, in the younger group comparison this effect was found in the control, but not the FESz group who responded to target and non-target stimulus similarly in the anterior and posterior region.

#### *5.5.2.1.2 Latency*

Topographical head maps for N100 latency to target and non-target stimuli, for control and clinical groups appear in Figure 5.13.

Chronic schizophrenia versus older controls

Left versus right

Effects were not significant for hemisphere or its interactions.

Anterior versus posterior

There was a significant effect for region,  $F(1,60) = 9.77$ ,  $p < .01$ , with N100 latency prolonged in the anterior compared with the posterior region. This effect was qualified by a Region X Stimulus significant contrast,  $F(1,60) = 11.51$ ,  $p < .001$  demonstrating that the regional effect on latency was maximal for the target compared with non-target stimulus. There were no significant interactions between-group and region.

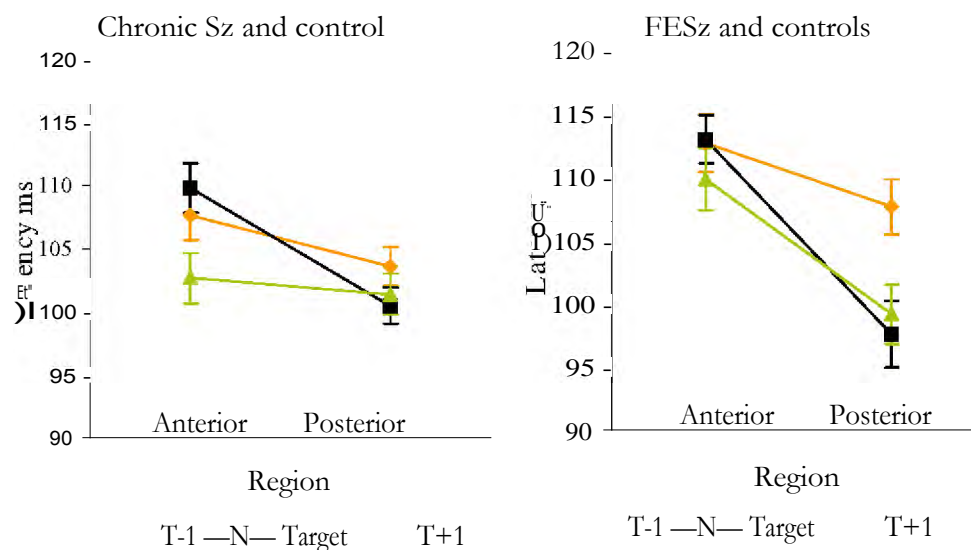


Figure 5.14 N100 latency to target and non-target stimulus at anterior and posterior regions.

FESz versus younger controls

Left versus right

Effects were not significant for hemisphere or interactions between hemisphere and group or stimulus.

Anterior versus posterior

There was a significant effect for region,  $F(1,60) = 34.98$ ,  $p < .001$ , with N100 latency prolonged in the anterior compared with the posterior region. This effect was qualified by a Region X Stimulus significant contrast,  $F(1,60) = 5.78$ ,  $p < .05$ , for the non-target comparison, as the region effect was maximal for the T+1 compared with T-1 stimulus. The target vs non-target contrast was not significant. As seen in Figure 5.13, this appears to be because N100 amplitude to T+1 stimulus is also increased. Group and region did not interact significantly.

Summary

Analysis by hemisphere and region revealed no between-group differences for N100 latency. All four groups showed a similar pattern of prolonged N100 latency to targets (compared with non-targets) especially at anterior sites.

### 5.5.2.2 P200

#### *5.5.2.2.1 Amplitude*

Topographical head maps for P200 amplitude to target and non-target stimuli, for control and clinical groups appear in Figure 5.15. The results of the statistical analysis are summarised in Table 5.14

Table 5.14 Summary of P200 amplitude results

		<i>Chronic Sz</i>		<i>FESz</i>	
df (1,59)	Stimulus	Location F	<i>p</i>	F	<i>p</i>
Hemisphere		L vs R			
Hemisphere X Group		L vs R			
Hem X Stimulus	T vs NTs	L vs R			
	T-1 vs T+1	L vs R	10.70	0.002	5.47
Hem X Stim X Grp	T vs NTs	L vs R			0.023
	T-1 vs T+1	L vs R			
Region		A vs P	5.68	0.020	35.49
Region X Group		A vs P			0.000
Region X Stim	T vs NTs	A vs P	12.01	0.001	4.62
	T-1 vs T+1	A vs P			0.036
Grp X Reg X Stim	T vs NTs	A vs P			
	T-1 vs T+1	A vs P			

Chronic schizophrenia versus older controls

Left versus Right

Effects were not significant for hemisphere or interactions between hemisphere and group. However, the Hemisphere X Stimulus interaction for the T+1 vs. T-1 contrast was significant indicating that P200 amplitude was larger in the left compared with the right hemisphere, to the T+1 stimulus (see Table 5.14, values in blue & Figure 5.16).

Anterior versus posterior

There was a significant effect for region, reflecting increased P200 amplitude in the posterior compared with the anterior region. This effect was qualified by a significant Region X Stimulus contrast for the target vs. non-target comparison, as the stimulus effect was maximal for the posterior region (see Table



5.14 values in green & Figure 5.16). There were no significant interactions between-group and region.

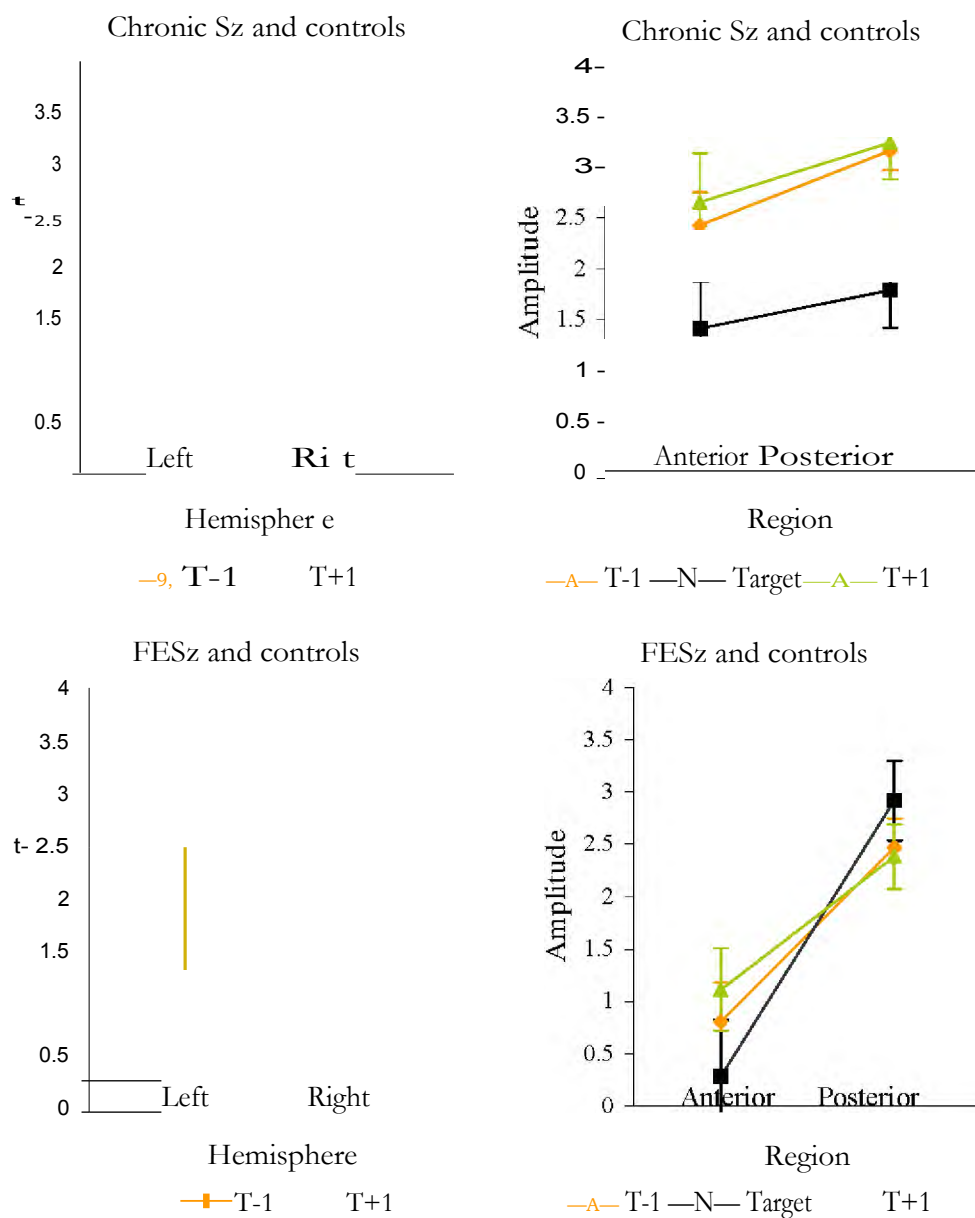


Figure 5.16 P200 amplitude to T-1 and T+1 stimulus, by hemisphere (left panels) and to target and non-target stimuli by region (right panels).

FESz versus younger controls

Left versus Right

Effects were not significant for hemisphere or interactions between hemisphere and group. However, the Hemisphere X Stimulus interaction for the T+1 vs. T-1 contrast was significant, indicating that P200 amplitude was larger in the left compared with the right hemisphere for the T+1 stimulus (see Table 5.14 values in blue & Figure 5.16).

Anterior versus posterior

There was a significant effect for region, indicating increased P200 amplitude in the posterior compared with the anterior region. This effect was qualified by a significant Region X Stimulus contrast for the target vs. non-target comparison, as the region effect was maximal for the target compared with the non-target stimulus (see Table 5.14 values in green & Figure 5.16). There were no significant interactions between group and region.

Summary

Across groups, P200 amplitude was maximal in the posterior region and increased to the T+1 stimulus on the left compared with right hemisphere.

#### 5.5.2.2.2 *Latency*

Topographical head maps for P200 latency to target and non-target stimuli, for control and clinical groups appear in Figure 5.17. The results of the statistical analysis are summarised in Table 5.15.



Table 5.15 Summary of P200 latency results

			Chronic Sz	FES z	
$4f(1, 59)$	Stimulus	Location	<i>F</i>		
Hemisphere		L vs R	--	4.30	.04
Hemisphere X Group		L vs R	4.67	.035	
Hemisphere X Stim	T vs NTs	L vs R	--	3.86	.05
	T-1 vs T+1	LvsR			
Hem X Stim X Grp	T vs NTs	L vs R			
	T-1 vs T+1	LvsR			
Region		A vs P	10.36	.002	10.86 .002
Region X Group		A vs P			
Region X Stim	T vs NTs	A vs P	--	4.45	.04
	T-1 vs T+1	A vs P			
Reg X Grp X Stim	T vs NTs	A vs P	6.49	.01	
	T-1 vs T+1	A vs P			

Chronic versus Older controls

Left versus Right

Effects were not significant for hemisphere or interactions between hemisphere and stimulus. However, the Hemisphere X Group interaction was significant, indicating that P200 latency delay in the older control compared with chronic schizophrenia group was maximal in the left hemisphere (see Table 5.15, values in blue & Figure 5.18).

Anterior versus posterior

There was a significant effect for region, with P200 latency prolonged in the anterior compared with posterior region. This effect was qualified by a Region X Stimulus X Group interaction with the target vs. non-target contrast significant, as the stimulus effect was maximal in the posterior compared with anterior region (see Table 5.15 values in blue & Figure 5.19).

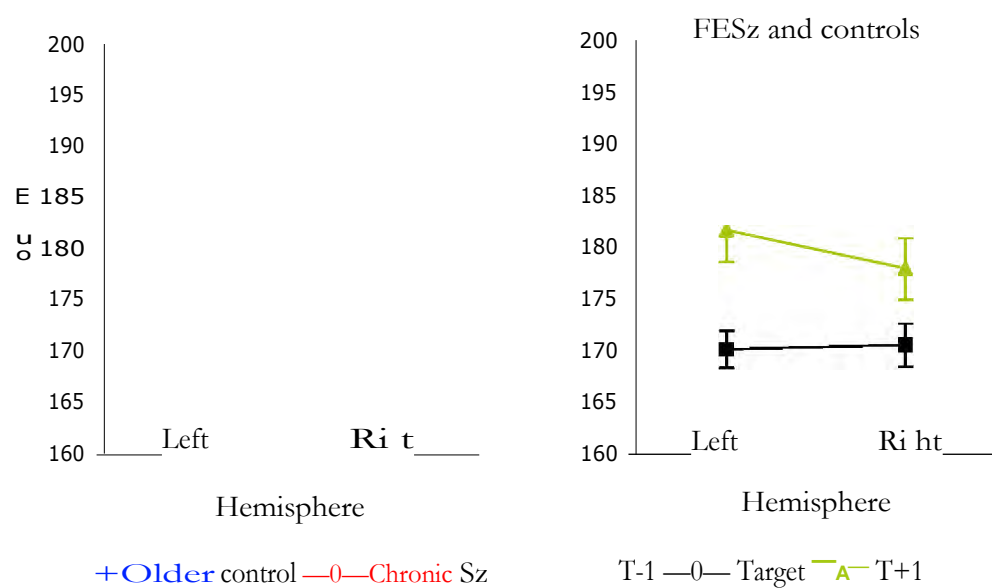


Figure 5.18 P200 latency across stimuli for chronic schizophrenia and older control groups, by hemisphere (left panel), and to target and non-target stimulus, across FESz and younger control groups, by hemisphere (right panel).

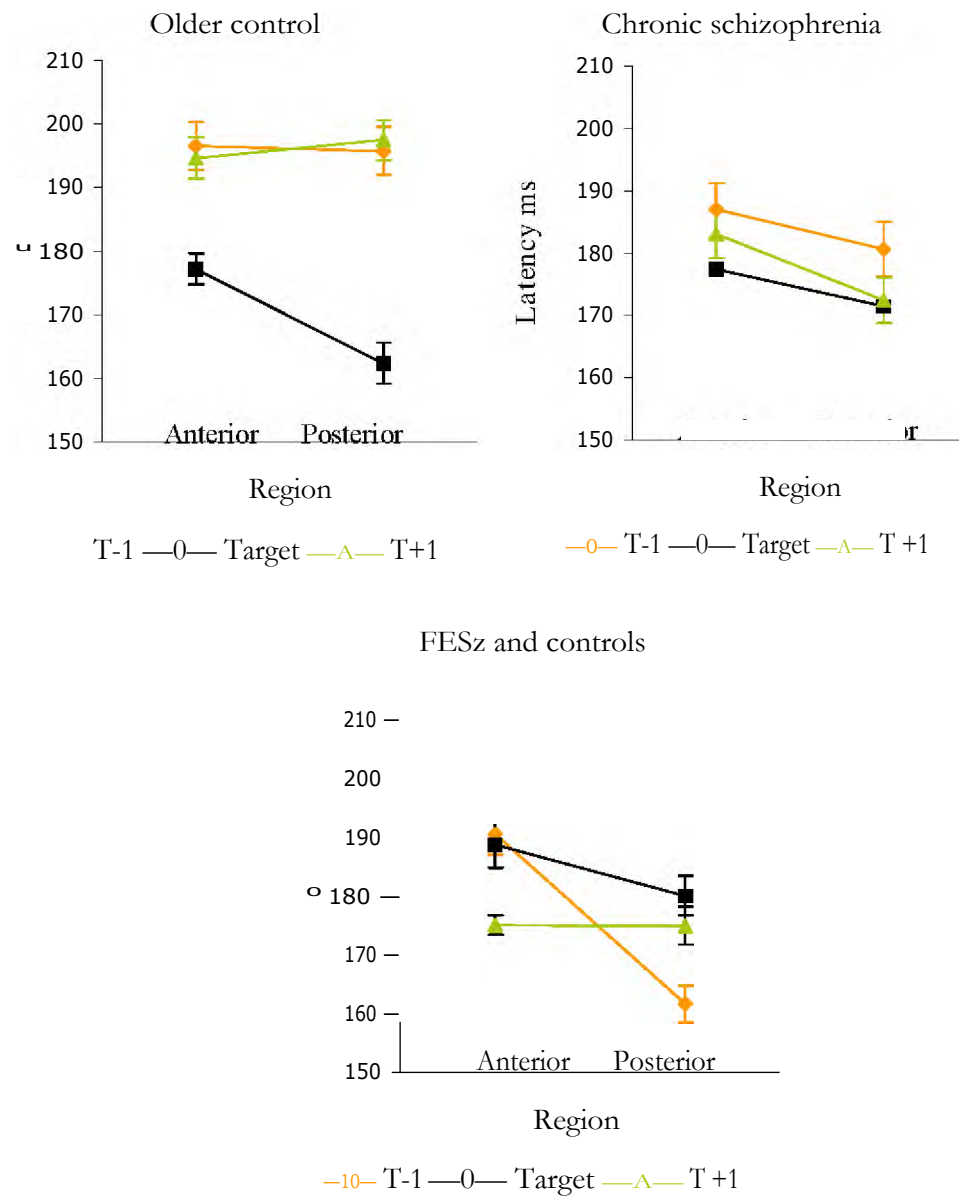


Figure 5.19 P200 latency to target and non-target stimulus in anterior and posterior regions, for chronic schizophrenia and older control groups (top panel) and across group for FESz and younger control groups.

## FESz

### Left versus right

There was a significant effect for hemisphere, signifying prolonged P200 latency in the left compared with right hemisphere. This effect was qualified by a Hemisphere X Stimulus interaction, with the target vs. non-target contrast significant, as the stimulus effect was maximal in the left compared with right hemisphere (see Table 5.15 values in green & Figure 5.18). There were no significant interactions between group and hemisphere.

### Anterior versus posterior

There was a significant effect for region, indicating prolonged P200 latency in the anterior compared with posterior region. This effect was qualified by a Region X Stimulus interaction, with the target vs. non-target contrast significant, as the stimulus effect was maximal in the anterior compared with posterior region (see Table 5.15 values in blue & Figure 5.19). There were no significant interactions between group and region.

### Summary

Delayed P200 latency in the anterior (compared with posterior) region was found over stimuli and groups. For the older controls (compared with chronic schizophrenic) the delayed P200 latency was found in target (compared with non-target) stimuli at anterior sites, and across stimuli on the left (compared with right) hemisphere. In the FESz and younger control groups, delayed P200 latency was evident to T-1 (compared with T+1) stimuli at anterior sites, and to non-target (compared with target) stimuli on the left (compared with right) hemisphere.

### 5.5.2.3 N200 component

Topographical head maps for N200 amplitude and latency to target stimuli, for control and clinical groups appear in Figure 5.20

Old control Chronic Sz



#### Anterior versus posterior

There was a significant effect for region,  $F(1,70) = 23.4$ ,  $p < .001$ , indicating increased N200 amplitude in the anterior (compared with posterior) region. This effect was qualified by a significant Region X Group interaction,  $F(1,70) = 11.51$ ,  $p < .01$ , suggesting that this pattern was mainly attributable to the chronic schizophrenia group (see Figure 5.21).

#### FESz versus younger controls

##### Left versus Right

There was a significant main effect for hemisphere,  $F(1,59) = 4.33$ ,  $p < .05$ , indicating increased N200 amplitude in the right (compared with left) hemisphere in both groups. Effects were not significant for the interaction between group and hemisphere.

#### Anterior versus posterior

There was a significant effect for region,  $F(1,60) = 88.8$ ,  $p < .001$ , with N200 amplitude increased in the anterior compared with posterior region, however this effect was qualified by a significant Region X Group interaction,  $F(1,60) = 4.36$ ,  $p < .05$ , suggesting that this pattern was maximal in the young control group (see Figure 5.21).

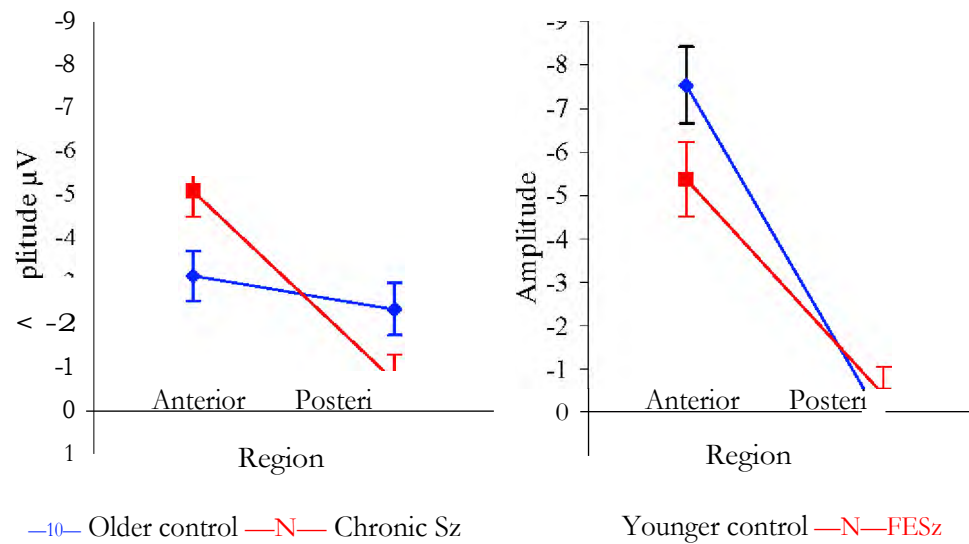


Figure 5.21 N200 amplitude at anterior and posterior regions.

#### 5.5.2.3.2 Latency

Chronic schizophrenia versus older controls

Left versus Right

Effects were not significant for hemisphere or the interaction between group and hemisphere for N200 latency.

Anterior versus posterior

There was a significant effect for region,  $F(1,70) = 12.06$ ,  $p < .001$ , with P200 latency prolonged in the anterior compared with posterior region. Effects were not significant for the Group X Region interaction.

FESz versus younger controls

Left versus right

Effects were not significant for hemisphere, however, there was a Group X Hemisphere interaction,  $F(1,59) = 5.38$ , as the younger control group were more delayed in the left compared with the right hemisphere whereas the FESz group were more delayed in the right compared with the left hemisphere. Hence the delay for the FESz group was more pronounced in the right hemisphere.

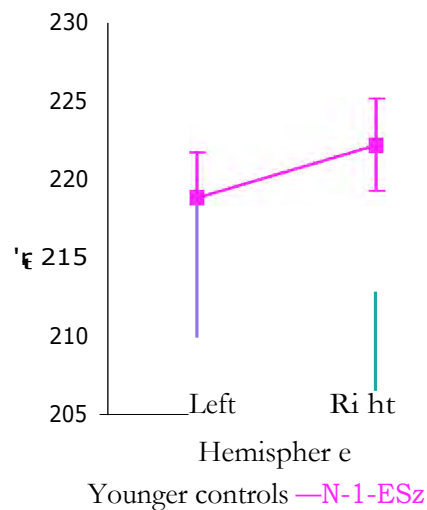


Figure 5.22 N200 latency for FESz and younger controls by hemisphere.

Anterior versus posterior

There was a significant main effect for region,  $F(1,59) = 67.46$ ,  $p < .05$ , with N200 latency delayed in the anterior compared with posterior region. Effects were not significant for the Group X Region interaction.

## Summary

Increased anterior compared with posterior N200 amplitude was found across all groups, however, this effect was stronger in the chronic schizophrenia group compared with older controls and in younger controls compared with FESz group. The FESz group showed the opposite pattern of hemisphere effects compared to their control group, displaying delayed N200 latency in the left hemisphere.

### 5.5.2.4 P300 component

Topographical head maps for P300 amplitude and latency to target stimuli, for control and clinical groups appear in Figure 5.23

Old control **Chronic Sz**

#### 5.5.2.4.1 Amplitude

Chronic schizophrenia versus older controls

Left versus Right

Effects were not significant for hemisphere, or the interaction between group and hemisphere, for P300 amplitude, nor was there a significant Group X Site interaction evident when the P300 amplitude analysis was restricted to T3 and T4 sites,  $F(1,72) = .02, p = .87$ .

Anterior versus posterior

The expected effect for region associated with P300 was observed,  $F(1,66) = 142.87, p < .001$ , indicating P300 amplitude was maximal in the posterior compared with anterior region. Effects were not significant for the Group X Region interaction.

FESz versus younger controls

Left versus Right

Effects were not significant for hemisphere or the interaction between group and hemisphere for P300 amplitude, nor was there a significant Group X Site interaction when the P300 amplitude analysis was restricted to T3 and T4 sites,  $F(1,66) = .01, p = .92$ .

Anterior versus posterior

There was a significant main effect for group,  $F(1,60) = 88.8, p < .001$ , indicating P300 amplitude was maximal in the posterior compared with anterior

region. However, this effect was qualified by a significant Region X Group interaction,  $F(1,60) = 4.36$ ,  $p < .05$ , suggesting that this pattern was maximal in the young control group (see Figure 5.24).

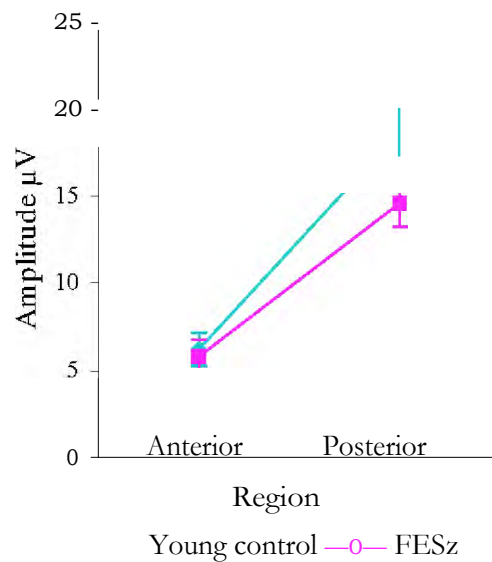


Figure 5.24 P300 amplitude by region for FESz and younger control groups.

#### 5.5.2.4.2 Latency

Chronic schizophrenia versus older controls

Left versus right

Effects were not significant for hemisphere or the interaction between group and hemisphere for P300 latency.

Anterior versus posterior

There was a significant effect for region,  $F(1,70) = 11.664$ ,  $p = .001$ , indicating that P300 latency was prolonged in the posterior compared with anterior region. Effects were not significant for Group X Region interaction.

FESz versus younger controls

Left versus right

Effects were not significant for hemisphere or the interaction between group and hemisphere for P300 latency.

Anterior versus posterior

Effects were not significant for region or the interaction between group and region for P300 latency.

Summary

Analysis for hemisphere did not produce significant between-group results for P300 amplitude or latency, for either of the two comparisons. A focussed analysis, did not find smaller P300s over the left (T3) site than over the right (T4) site in either the chronic or FESz groups (compared with normal controls). Analysis by region, demonstrated a generally increased and delayed P300, in the posterior (compared with anterior) region across the older control and chronic schizophrenia groups.

### 5.5.3 Response time

Both the chronic schizophrenia group (mean = 405ms, SD = 10ms) and the FESz group (mean = 367ms, SD = 9ms), showed significantly slower response

times ( $df=1,78$ ,  $p<.001$  and  $df=78$ ,  $p<.01$  respectively) than their normal controls (mean = 315ms, SD = 15ms; mean = 308ms, SD = 9ms). There were no significant differences between the chronic schizophrenia and FESz groups, or between the two control groups. Control groups averaged 99.8% (older) and 99.9% (younger) accuracy and the clinical groups averaged 93% (chronic schizophrenia) and 96.2% (FESz) accuracy

## 5.6 DISCUSSION

Results from this Study strongly suggest that abnormalities in ERPs in schizophrenia are not restricted to target stimuli, but occur to both target and non-target stimuli, and are evident at both the onset of schizophrenia and the chronic state of the illness. The results are, therefore, consistent with the hypothesis that ERP deficits in schizophrenia are trait like and not due to secondary effects of chronic morbidity, neuroleptics or institutionalisation. The examination of ERP responses to target and non-target stimuli, and further to T-1 vs. T+1 non-target stimuli, produced striking results. The chronic and FESz groups did not demonstrate the differential N100 and P200 amplitude responses to target and non-target stimuli shown by both older and younger control groups. In addition the chronic schizophrenia group did not differentiate in their response to T-1 and T+1 non-target stimuli for N100 amplitude, as did the older and younger control groups. Most importantly the stepwise discriminant function analysis demonstrated a superior classification for both chronic and FESz using the early components to both target and non-target stimuli in comparison to the previous focus on the P300 component elicited by target stimuli. The inclusion of ERP components to non-target stimuli, in addition to target



stimuli also provided evidence of differential aging effects on ERPs in schizophrenia versus normal controls and the most robust correlation with symptom factors.

*Schizophrenia versus Controls:* For both the chronic schizophrenia and FESz groups, the traditional averaged ERP to target stimuli showed decreased N100, N200 and P300 amplitude and increased P200 amplitude when compared to their controls. The reduced N100, N200 and P300 amplitude are consistent with previous ERP studies with schizophrenia (Ogura et al., 1991; Boutros et al., 1997; Brown et al. 2000) and with previously reported reduced N200 and P300 amplitude findings in FESz studies (Demiralp et al., 2002; Hirayasu et al., 1998; Salisbury et al., 1998). Previous target P200 amplitude findings have been mixed, however, the increased P200 amplitude in this Study replicates findings by Ogura et al. (1991) in an unmedicated sample. P200 amplitude has been reported to reflect aspects of decision-making or stimulus encoding (McCarley et al., 1991).

There were some differences, however between the chronic schizophrenia and FESz groups and their respective controls. While amplitude disturbances were common to both groups, latency deficits were specific to the chronic group, who showed delayed P200 and N200 latencies to targets, and earlier P200 latency for non-targets. The FESz group, in contrast, showed no significant latency differences in comparison to their control group. One possible explanation for this pattern of results is that the observed amplitude deficits manifest an association with more primary aspects of the disease, whereas latency differences represent secondary or subsequent aspects, for example, direct consequences associated with the progression of the disease or indirect consequences of chronicity such as institutionalisation. In

addition, the reduced P200 amplitude to T+1 stimulus found in the FESz was not found in the chronic schizophrenia group.

*Target versus non-target:* The disturbance in information processing is also elucidated by within group comparisons. The pattern of significant differences between targets and non-targets (smaller earlier P200 to targets versus increased delayed P200 to non-targets), shown by the controls, was not shown either by the chronic schizophrenia or FESz groups (see Figures 5.2 and 5.4). In the chronic schizophrenia group, P200 amplitude and latency did not vary significantly between target and non-target stimuli. In the FESz group, P200 amplitude either did not differentiate at fronto-central sites, or differentiated by increasing to target (compared with non-target) stimuli at the parietal site. This is in the opposite direction to the control group, where P200 amplitude is reduced to target (compared with non-target) stimuli. The FESz group, showed a shift in P200 latency between target and non-target stimuli. Scrutiny of the waveforms (Figure 5.1) suggests that the P200 amplitude and latency shift between targets and non-targets, shown by the controls, may result from the overlap with the N200 components in ERPs to target stimuli. Thus, the large and wide P200 amplitude component normally elicited by non-target stimuli is reduced and narrowed by the negative shift associated with the N200 component in ERPs elicited by target stimuli. It is possible that this does not occur to the same extent in the chronic and FESz groups because their N200, and P300 components are reduced compared to controls, and so the N200 overlap is not so prominent in the P200 component. This would contribute to the larger P200 amplitude to targets found in the chronic schizophrenia group compared to controls. It should be noted, however, that the P200 amplitude produced by the target stimuli

is actually *larger* than the P200 amplitude produced by the non-target stimuli in the FESz group *despite* the presence of the N200 component in the target elicited ERP. Although not within the scope of this thesis, a new single trial method (Melkonian et al., 2001) will be applied to this data to tease out the overlapping components to investigate, amongst other questions, whether P200 differences remain when the effects of the N200 overlap are removed.

The N100 component is correlated with specific aspects of stimulus features (Pritchard, 1986; Naatanen and Picton, 1987), but may also reflect attention, as it is generally larger with increasing attentional requirements (Maclean et al., 1975). It is also affected by non-specific arousal (Rockstroh, Muller, Wagner, Cohen, & Elbert, 1994). The chronic and FESz groups, in addition to showing an overall reduction of N100 amplitude, also failed to show the distinct pattern of N100 amplitude to target >T-1 > T+1 stimuli found in the control groups. The stimulus features of the T+1 and T-1 stimuli are identical. It is therefore possible that the reduction in N100 amplitude to T+1 stimuli found in normal controls, but not in patient participants, could be due to temporal recovery, as the T+1 stimuli follows a target that requires a cognitive and motor response. Alternatively, it could reflect reduced attentional requirements for T+1 stimulus due to changes in states of vigilance or preparedness, as a target stimulus is always followed by a non-target stimulus in this paradigm. This possibility is further explored in Study 3, employing a paradigm in which target stimuli are equiprobably followed by target or non-target stimuli. Further support for this proposition comes from the results of an associative learning study utilising visual stimuli, in which the N100 amplitude evoked by a stimulus 2(S2) following a predictive stimulus 1(S1) was reduced (Rose, Verleger, & Wascher, 2001). The

authors interpreted this reduction as indicative of a reduced need to allocate spatial attention to S2 because S1 had provided reliable information about S2. If this interpretation is accurate, the results of the present Study would indicate that a similar process applies to the auditory attentional system

The patient group's diminished discrimination between target and non-target stimuli (and also between T-1 and T+1) suggests that they are less flexible in differentiating and processing target and inhibiting non-target information than controls. This pattern is consistent with Gray's (1998) model in which "misattributions" in the match/mismatching of target: non-target information is proposed to underlie the core positive symptoms in schizophrenia. A failure to develop an expectancy that a non-target would follow a target could be further evidence of this dysfunction, and may stem from the failure to make use of stored regularities in information processing. Amongst other possibilities, it may be viewed as a disturbance in implicit memory.

N100 amplitude was robustly correlated with the disorganisation factor for both the chronic and FESz groups. As disorganisation increased, N100 amplitude reduced. As predicted, this correlation was stronger for non-target stimuli in comparison to target stimuli. Perhaps increased disorganisation in schizophrenia is more strongly associated with the failure to inhibit, or dampen the processing of irrelevant stimuli (non-targets) than it is related to preferential processing of relevant stimuli (targets). These findings indicate that the reduced N100 amplitude in schizophrenia is present at the onset of illness, as well as later chronic stages. This reduction to non-target stimuli related to disorganisation, the putative core factor of schizophrenia.

Increased N100 amplitude to non-target stimulus and decreased and delayed P300 component to target stimulus with age are robust findings (see 4.1.1) and were found in the combined (younger + older) normal control group in this Study. In the combined schizophrenia group, however, correlations were not significant between age and both N100 amplitude and P300 latency. For P300 amplitude the correlation only just reached significance. Further differential age effects were found for P200 latency. The control group showed prolonged P200 latency to non-target stimuli with age, whereas the schizophrenia groups showed prolonged P200 latency to target stimuli with age. The combined normal control group also demonstrated a decrease in N200 amplitude with age, an effect not found in the schizophrenia groups. These results do not suggest the accelerated ageing that would be expected with a neurodegenerative illness. The pattern of results, including the absence of age effects, along with the presence of similar deficits in both first episode and chronic schizophrenia, are more consistent with a neurodevelopmental hypothesis.

Compared to the N200 and P300 components, which have been the focus of schizophrenia research, the N100 and P200 components acquired in response to both targets and non-targets provided a more accurate classification for both the chronic schizophrenia group (improved from 75% to 82.5%) and the FESz group (improved from 62.5% to 82.5%). Thus, the emphasis on extending ERP investigations to components other than P300 in the current Study is strongly supported.

Perceptual abnormalities are an early sign of the onset of psychosis (Chapman, 1966) and the development of investigational methods to assess this is important. Given the current emphasis in first episode psychosis treatment on early

identification and active treatment of young people at risk (McGlashan 2001a, McGlashan 2001b), a method to help highlight risk prior to a psychotic episode, and track treatment progress is necessary. For these purposes, and to avoid unnecessary use of antipsychotic medication, it is imperative to correctly differentiate FESz patients from normal and other non-psychotic controls. The benefit of using the earlier components to target and non-target stimuli is illustrated by the reduction in false positive classifications i.e. 37.5% of the controls would have been falsely classified as FESz using the N200 and P300 components to target stimulus versus 20% using the N100 and P200 components to both target and non-target stimuli. However, because this Study did not use a clinical control group, the specificity of these findings needs to be examined.

Gender effects did not differ for the schizophrenia group compared with controls for N100 amplitude and latency or P200 amplitude. However, males with schizophrenia (both first episode and chronic) compared with females, showed shorter P200 latency to target compared to non-target stimuli. This effect was maximal at the central site. In addition, the reduced N200 amplitude in the chronic schizophrenia compared with the control group arose predominantly from a reduction in females in the schizophrenia group. These were unexpected findings, as one might expect gender differences in schizophrenia to favour females rather than males. Previous schizophrenia research has indicated improved outcomes for females compared to males (Tamminga, 1997; Castle et al., 2000), suggesting that females appear to have a less virulent form of the disorder (Flor-Henry, 1985; Andia et al., 1995; Kulkarni, 1997).

Overall there were few group topographical differences. The left lateralised P300 amplitude deficit found in some studies (see Chapter 4.5) did not occur, even when restricting the comparison to T3 and T4 electrode sites. The left lateralised P300 deficit has been found more commonly in studies using a count response than button press. It is possible, therefore, that the button press response used in this Study has contributed to the absence of the lateralised P300 amplitude deficit, although Turetsky et al. (1998) has demonstrated this lateralised deficit, using the button press. Another possible contributing factor is that the EEG recording was not acquired from TCP1 and TCP2 sites which were found to show a greater effect than T3 and T4 in a meta- analysis of P300 topography studies (Jeon & Polich, 2001).

In conclusion, this Study found that:

- (i) N100 and P200 target versus non-targets differences and non-target sequence effect differences (T-1 vs. T+1) are diminished in schizophrenia.
- (ii) In comparison to target generated P300 amplitude, N100 and P200 deficits to target and non-target stimuli show improved *sensitivity* for schizophrenia.

These findings led to further investigations in subsequent studies. The next Study (Chapter 6) explores whether sequence effects on ERPs to target stimuli, as well as non-target stimuli, are disturbed in first episode schizophrenia. It also examines whether N100 non-target (T-1, T+1) sequence effects are found when target stimuli are equiprobably followed by a target or non-target stimulus. Study 4 (Chapter 7) focuses on the important issue of whether these findings are specific to first episode schizophrenia, compared to a clinical control group (ADHD) in which P300 amplitude has also been found to be reduced.

## 6 ERP SEQUENCE EFFECTS IN FIRST EPISODE SCHIZOPHRENIA

### 6.1 INTRODUCTION

Studies 1 and 2 (Chapters 3 & 5) suggested a problem in schizophrenia, with either the independent processing of target and non-target stimuli, and/or the interactional effects emerging from the ongoing processing of these two stimuli. These findings were robust, present at the first onset of illness and also in chronic schizophrenia, and consistent with preliminary findings in the literature. This problem could underlie the core information processing problems in schizophrenia and may link ERP findings to investigations using alternate methodologies, for example, deficits in latent inhibition and Kamin Blocking in people with schizophrenia and their first degree schizotypal and non-schizotypal relatives (Baruch, Hemsley, & Gray, 1988; Jones, Gray and Hemsley, 1992; Martins, Jones, Toone, & Gray, 2001). Latent inhibition is a weakening of associative learning if the 'to be conditioned' stimulus is first pre-exposed a number of times without any consequence. Similarly, in Kamin Blocking, pre-exposure to a first association between a conditioned (CS1) and unconditioned stimulus (UCS), results in a block to the learning of a compound stimulus (CS1 + CS2), followed by the same UCS. Deficits on these tasks are interpreted as possibly arising from a basic impairment in associative learning, also suggesting that the association between two stimuli are not processed accurately in schizophrenia.

The Gray-Hemsley model (Gray, Feldon, Rawlins, Hemsley, & Smith, 1991; Gray, 1998; Hemsley, 1993, 1994) proposes that people with schizophrenia fail to establish appropriate response biases because they are unable to use stored memories



of regularities based on their previous experience. This results in a failure to make use of temporal and spatial redundancy to reduce information processing demands. Although the Gray-Hemsley model is derived from empirical research in a different field, it is worthwhile and intriguing to determine whether the same dysfunctional mechanisms postulated might underlie observed ERP deficits in the auditory oddball paradigm. To this end, the current Chapter will investigate P300 and reaction time to target stimuli, and N100 amplitude to non-target stimuli, on tasks involving repetition of two stimuli: target (T) and non-target (N).

As ERP deficits are found in schizophrenia at first episode (Study 2, Chapter 5) it was decided to investigate a group with first episode schizophrenia to reduce confounding effects which may be secondary to chronic morbidity, such as prolonged use of neuroleptic medication, or hospitalisation.

#### 6.1.1 Sequence effects on P300 and RT

Attempts to examine the relationship between two repeating stimuli presented in random sequence have been made in studies examining sequence effects. In these studies, the sequential structure of stimuli preceding the target stimuli has been consistently shown to affect target response. For example, subjects tend to respond more quickly to the continuation of a stimulus repetition (TT), than to its discontinuation (NT). Studies which have examined sequence effects have in general, either used a simple RT task, where the subject is asked to respond to targets and ignore non-targets, or a choice reaction time task (CRT), in which different responses (e.g. left vs. right button presses) are required to targets and non-targets.

Sequence effects were first demonstrated in reaction time (Remington, 1969) and have been robustly replicated (Kirby, 1976, 1980; Soetens, Boer, & Heuting, 1985; Soetens, Deboek, & Hueting, 1984). It was found that RTs were influenced, not only by the current stimulus, but also by the sequence of preceding stimuli. Two types of sequence effects are observed in choice RT tasks. First order effects are attributable to the immediately preceding event, whereas higher order effects are caused by events earlier in the sequence (Kirby, 1980; Soetens, Boer, & Heuting, 1985). Both these effects are dependent on the response-stimulus interval (RSI), the interval from the preceding response to the next stimulus presentation. For first order effects, RTs are shorter for repetitions than alternations ( $T^*T < NT^*$ )<sup>4</sup> at RSIs less than 500ms, and shorter for alternations than for repetitions ( $NT^* < T^*T$ ) when RSIs are longer than 500ms (Hale, 1967; Kirby, 1976; Soetens, Boer, & Heuting, 1985; Soetens, Deboek, & Hueting, 1984). Higher order sequential effects are observed after continued runs of stimulus repetitions or stimulus alternations ( $T^*T^*T^*T^*$  or  $N^*T^*N^*T^*$ ), or conversely discontinuations of these runs ( $NNNT$  or  $NTNTT$ ), with faster RTs to continuations than to discontinuations (Remington, 1969; Soetens Boeing, & Hueting, 1985). At shorter RSIs, these patterns, referred to as cost-benefit patterns, are not found; instead a benefit only pattern is found (Kirby, 1976; Soetens, Deboek & Hueting, 1984; Vervaeck & Boer, 1980). The cost-benefit patterns found with long RSIs were explained by confirmations and disconfirmations of expectancies, arising

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<sup>4</sup> Various terminologies have been used for the two alternate stimuli in sequence studies, for example, A/B, A/R, and NIT. To avoid confusion the two stimuli will be referred to as T and N in this thesis. When used with a CRT task, T and N refer to the two alternate target stimuli, when used with a simple RT task the T refers to the target stimuli and the N refers to the non-target stimuli.

from the preceding sequence of stimuli. If expectancy is confirmed, RT is short, and if it is disconfirmed, RT is long.

Squires, Wickens, Squires and Donchin (1976) demonstrated that ERPs also reflected sequence effects. Thus, in addition to RT as an index of performance, ERPs might also provide an index of the underlying psychophysiology. These studies, and others (Duncan-Johnson & Donchin, 1982, Johnson & Donchin, 1980), demonstrated that target stimuli that continue a series of repetitions (TT, TTT, TTTT, or alternations (NT, NTN, NTNT) elicit smaller P300s and earlier RTs than target stimuli that discontinue a sequence of repetitions ( T), or alternations (NTNTT). Most low probability oddball studies average over sequence types, thereby losing valuable information when sequences have been a determinant of P300 amplitude.

A methodological issue that deserves mention, is that most of the earlier sequence studies (Duncan-Johnson, Roth, & Kopell, 1984; Duncan-Johnson & Donchin, 1982, Johnson & Donchin, 1980; Squires, Wickens, Squires, & Donchin, 1976) examined sequence effects in a hierarchical cumulative manner, where first order effects, attributable to the immediately preceding event (e.g. TN), include higher order effects, events that are earlier in the sequence (NNT, TNT, NTNT, TTNT etc.). For example, Duncan Johnson et al., 1984 used a Group X Stimuli X Sequence (repetition vs. alternation) X Outcome (continuing vs. discontinuing) X Site analysis. This hierarchical cumulative approach does not facilitate analysis of lower vs. higher order effects (NT vs. NNT vs. NNNNT) which are the focus of this Study.

Mean ERP scores to different sequences, commonly visually presented as "sequence trees" in sequence studies (Duncan-Johnson et al., 1984, Johnson & Donchin, 1980; Squires, Wickens, Squires, & Donchin, 1976) indicate that in addition to the 'continuation versus discontinuation' and 'alternation versus repetition' comparisons, there appear to be linear relationships within these series, for example, consistent linear increases in P300 amplitude to discontinuation of repetition or *DR* series ( $DR5 > DR4 > DR3 > DR2 > DR1$ ) and perhaps more minimally to discontinuation of alternations ( $DA3 > DA2 > DA1$ ). However, because of the statistical approach mentioned above, the significance of these possible linear relationships has not been tested. In normal controls, RT appears to decrease within the *DR* series (Duncan-Johnson et al., Gonsalvez et al.) and increase with the *DA* series (Duncan-Johnson et al.). The P300 latency results across *DR* or *DA* series have been examined infrequently.

As sequence manipulations resulted in effects on both RT and P300 amplitude, initial efforts sought a single explanation for both effects. For example, the expectancy model that was used to explain the cost-benefit pattern in RT results, was generalised to ERPs (Duncan-Johnson & Donchin, 1982, Johnson & Donchin, 1980; Squires, Wickens, Squires, & Donchin, 1976). However, the expectancy explanation of sequence effects has now been challenged from a number of directions. Sequential effects in RTs show properties that are not explainable by expectancy (Soetens et al., 1985). In the stimulus repetition effect, for example, faster RTs for repetitions than alternations with a faster stimulus presentation rate, have been associated with an automatic facilitation or priming, rather than the

subjective expectancy associated with slower presentation rate (Kirby, 1980; Soetens, 1998; Soetens et al., 1985).

Studies showing evidence of dissociation between sequence dependent RT and P300 amplitude patterns (e.g. some experimental manipulations have produced RT and ERP results in opposite directions) have challenged the idea of a common expectancy mechanism for RT and P300 amplitude sequence effects (Leuthold & Sommer, 1993). The effects of "practice" (Sommer et al., 1990) and "manipulated expectations" (Matt, Leuthold, and Sommer, 1992) have been found in RTs, but were absent (practise), or minimal (manipulated expectancies) in P300 amplitude. Leuthold & Sommer (1993) found that the first order repetition effect in P300 amplitude was only observed at a 1.3 sec ISI, and not at slower presentation rates, whereas higher order effects were unmodulated by ISI. P300 amplitude is usually smaller, whereas RT may be longer for first order repetitions, as compared to alternations (Sommer, Leuthold and Soetens 1999; Sommer, Leuthold, & Matt, 1998). In higher order sequential effects, Sommer, Leuthold and Soetens (1999) found the sequential pattern in RTs changed from cost-benefit to cost, only when RSI was decreased from 500 to 40ms, whereas P300 consistently showed a cost-benefit pattern at both RSIs.

Other findings have also challenged the expectancy hypothesis. Sommer, Matt, & Leuthold (1990b) showed that conscious expectancies for a given stimulus, as measured by subjective ratings, are barely affected by the trial sequence. The ability to develop trial to trial expectancies would presumably rely on being able to encode and hold in immediate memory the recent stimulus pattern, in order to

categorise the current stimulus as locally frequent or rare, yet P300 sequence effects have been found in groups with diminished immediate memory capacity and function (Polich and Broderant, 1997).

The above reasons have led researchers to question the notion that expectancy disconfirmation underpins observed variations in P300 amplitude (e.g. Verleger, 1988; Gonsalvez et al., 1999; Gonsalvez & Polich, 2002; Croft, Gonsalvez, Gabriel, & Barry, 2003). Gonsalvez and colleagues (Gonsalvez et al., 1999; Gonsalvez & Polich, 2002; Croft, Gonsalvez, Gabriel, & Barry, 2003) suggest an alternative explanation for at least some sequence effects, arguing that the first order, or stimulus mismatch versus stimulus match effect (NT vs T<sup>\*</sup>T), and the higher order discontinuation of repetition (*DR*) series or non-target sequence length effect (NNNT vs. NNT vs. NT) upon P300 amplitude are the result of target-to-target interval (TTI) rather than sequence effects. This hypothesis is explained by resource limitation, i.e. P300 updating processes are primarily influenced by the interval between stimuli rather than the sequence structure context effects (Gonsalvez & Polich, 2002).

#### 6.1.1.1 *DA* effects on ERPs: Are they an index of cognitive processes implicated in associative learning?

Several sequence studies have found an interesting relationship between P300 amplitude and discontinuation of alternation (*DA*) series. *DA* effects occur where a preceding alternation or series of alternations is terminated by a repetition of the penultimate stimuli, thus discontinuing the alternation pattern as in the following: NTT (*DA1*); NTNT<sup>\*</sup>T (*DA2*); NTNTNTT (*DA3*). Although not as dramatic as *DR*

effects, *DA* effects have been reported in several studies (Duncan-Johnson et al., 1984; Squires et al., 1976) in a consistent direction, with P300 amplitude increasing with increases in the number of alternations preceding the final stimulus mismatch ( $DA3 > DA2 > DA1$ ). The *DA* effect on P300 amplitude cannot be explained by the  $T^*TI$  hypothesis, as  $T^*TI$  remains unchanged with increases in *DA* series.

Previous studies have explained alternation and *DA* series by invoking expectancy theory. The subject expects alternations to continue, larger numbers of alternations increase this expectancy, leading to reduced P300 amplitude. The final repetition violates this expectancy, leading to larger P300 amplitude (Duncan-Johnson et al., 1984; Squires et al., 1976). Regardless of whether expectancy underlies the *DA* effect, available evidence points to the fact that ERPs are sensitive to pair-wise occurrences of stimuli or to the relationship between contiguous occurrences of stimuli. The brain (consciously or unconsciously) recognises a pattern of two alternating stimuli and responds differently when this pattern is continued versus when it is discontinued. In addition, the number of preceding pairs appears to influence P300 amplitude in a consistent way, leading to the intriguing prospect that ERPs may be an objective measure of strength of associative coding. This possibility opens up a large number of exciting research avenues with significant clinical and theoretical implications. For example, if P300 to certain sequence types is indicative of associate encoding strength (at least in paradigms that elicit these sequence effects), reduced P300 may indicate poor encoding of stimulus pairs. This may underlie the widespread P300 amplitude deficit amongst people with schizophrenia, on oddball tasks. Poor encoding of contiguous occurrences of events could also explain latent inhibition and Kamin blocking results, and may be a core

cognitive deficit of schizophrenia. There are advantages in determining an objective measure of this, including an understanding of the psychophysiology of this deficit, as well as the provision of a biological marker for the disorder.

There is some support for the use of P300 as a correlate of associate learning from a study which isolated associative cognitive learning from non-associative adaptive mechanisms (Rose, Verleger, & Wascher, 2001). In this Study, amplitude of P300 evoked by the predictive first stimulus (S1) increased linearly over blocks, and P300 amplitudes, evoked by the second stimulus (S2) following the predictive S 1, decreased in the course of learning with a quadratic trend, while there were no modifications to P300 on the control task. The authors interpreted these trends as a fast decrease in neglecting the information of S2 and a continuous increase of the meaning of S 1.

An expectancy effect, based on paired associations, would predict that the increase in P300 amplitude to the terminating target in DA series compared to alternation series (which should be a decrease, according to TTI, as it immediately follows a target) is caused by a disconfirmation of this expected association. As it would take more than one pair to establish this association, this would be seen in linear increases of P300 amplitude within DA series. Previous studies have used shorter series (Duncan-Johnson et al., 1984 Squires et al., 1976) A systematic investigation of the effects of increasing DA series, may therefore, require longer series of stimuli than those normally used in sequence studies.



The primary focus of this Study was to examine the effect of increasing levels of *DA* series on the P300 component and RT of patients with FESz and normal controls. The current Study predicted that, in normal controls, there would be linear increases in P300 amplitude as a function of increases in the *DA* series, as suggested by a few earlier studies (Duncan-Johnson et al., 1984; Squires et al., 1976), reflecting appropriate associative encoding for stimulus pairs. It was hypothesised that this P300 amplitude pattern would not occur in the FESz group, indicating a problem with associative encoding. On the other hand, linear increases in *DR* series effects were predicted to occur in both the control and FESz group, according to the TTI hypothesis and previous findings (Duncan-Johnson et al., 1984; Gonsalvez et al., 1995). To examine these hypotheses, a specialised version of the oddball paradigm that included *DA* sequences ranging from *DA1* to *DA3* was developed.

#### 6.1.2 Sequence effects on P300 and RT in schizophrenia

Sequence effects on the P300 have been well established in normal healthy subjects. However, there has been a dearth of sequence effects studies in schizophrenia, with only two studies (Duncan-Johnson, Roth and Kopell, 1984; Gonsalvez et al. 1999) evident. One reason is that ERPs to each stimuli type need to be sub-averaged separately, and signal-to-noise requirements result in lengthy paradigms that are difficult for clinical populations, including schizophrenia, to complete. The Duncan-Johnson et al. study investigated sequence effects in a schizophrenia group, with a 0.5 probability CRT, where subjects responded to each of two tones by pressing one of two buttons. Although special attention was not paid to the *DA* series, the authors reported a similar overall pattern (sequence tree) of

P300 amplitude and RT changes in both the schizophrenia and normal control groups. The authors interpreted these ERP findings as an indication that people with schizophrenia formulate trial to trial expectancies, with RT findings indicating that these expectancies were applied to response preparation processes.

At first glance the above results would not appear to support the Gray-Hemsley model, or suggest that ERPs do not reliably index the deficit that these models hold as central to schizophrenia. It would suggest that people with schizophrenia accurately encode recent stimulus patterns and can categorise and respond to the next stimulus as locally frequent or rare, i.e. make connections between previous stimuli which then bias their response to the next incoming stimuli. On the other hand, it could be argued that the Gray-Hemsley model refers to "reliable" associations between stimuli, whereas the sequence effects refer to "random" stimuli. Of importance is the fact that the Gray Hemsley model applies more specifically to *DA* effects and *DA* effects were not examined by Duncan-Johnson et al. (1984) in a comprehensive manner. Consequently the results may have been swayed by the *DR* or other sequence types (where the schizophrenia group showed a similar pattern as normal controls), which could be attributed to *TII*, rather than by the *DA* series.

Gonsalvez et al. (1995) examined sequence effects in schizophrenia utilising a simple reaction time auditory oddball paradigm. Subjects responded (button press) only to target stimuli, separated by equiprobable series of 1,3,5,7,9 or 11 non-targets (1.3 seconds fixed ISI) with a 0.16 probability for target stimuli. Target ERPs were subaveraged according to the number of preceding non-targets, similar to stimuli in

*DR* series, but differing in extending the length of the sequence, with *DR* ranging from *DR1* through to *DR9*. Where the previously quoted studies had analysed the statistical difference between continuation and discontinuation of sequences, this Study examined whether P300 amplitude and RT varied in a linear way as *DR* series was manipulated, ranging from *DR1* to *DR9*. P300 amplitude increased with increasing numbers of non-targets preceding the target in schizophrenia patients as well as controls, however the reduction in P300 amplitude for the schizophrenia group compared with the control group was only significant to the target stimuli following non-target series of intermediate length (i.e. preceded by 3, 5 or 7 non-targets) and not when targets followed a short (1) or long (9) series of non-targets. Thus both studies (Duncan-Johnson et al.; Gonsalvez et al.) indicated a linear effect for *DR* series in schizophrenia, although Gonsalvez et al. was the only study to test this statistically.

### 6.1.3 Sequence effects on N100 amplitude

Most sequence studies have focused on the P300 component elicited by target stimuli. However, there are a number of studies which have found sequence effects on N100 amplitude to non-target stimuli (Hermanutz, Cohen, & Sommer, 1981; Hirata & Lehmann, 1990; Brown et al., 2002; Roth & Cannon, 1972; Starr, Aquinaldo, Roe and Michalewski, 1997; Staff, Sandroni & Michalewski, 1995). These studies all used simple RT rather than CRT tasks. Several studies (Hermanutz et al.; Hirata & Lehmann; Starr, Aquinaldo et al.; Starr, Sandroni et al.) have found a repetition effect demonstrating increasing N100 amplitude to non-target stimuli with longer trains of preceding non-targets. This is the opposite pattern to P300 amplitude to target stimuli which decreases with longer trains of preceding target stimuli (see

6.1.1). The results of Study 2 in this thesis demonstrated another sequence effect on N100 in normal controls; a reduction in N100 amplitude to  $T+1$  compared to  $T-1$ , an effect found in normal populations in some other studies (Roth & Cannon; Starr, Aquinaldo et al., Starr, Sandroni et al.) These studies have used oddball paradigms where target frequency is low and occurrences of  $T$ 's are absent. A study that examined changes associated with all four 2<sup>nd</sup> order sequence effects ( $T$ 's  $N$ 's,  $NN$  &  $TN$ ) did not find significant effects on N100 amplitude (Polich & Broderant, 1996). This suggests that the reduction to  $T+1$  compared to  $T-1$  stimuli may not be found when target stimuli may be followed by either target or non-target stimuli

Study 3 also sought to determine whether the reduction in N100 amplitude to  $T+1$  compared with  $T-1$  stimuli found in the control, but not the schizophrenia group in Study 2 (Chapter 3), was related to recovery cycle effects. If N100 amplitude reduction to  $T+1$  stimuli was attributable to recovery following a target, it should also be found in the paradigm used in this study using the same ISI as in S2, but with target probability raised to 0.5. Consequent to the probability manipulation, in Study 3, the  $T+1$  stimulus would no longer remain predictable as it could now be either a  $T$  or  $N$ , unlike in Study 2 where it was always an  $N$ . Therefore, if Study 3 replicated results of Study 2 (N100 amplitude to  $T+1 < T-1$ ) the recovery hypothesis would be supported, whereas if it did not, alternative explanations would have to be considered, for example, the predictability of the stimulus.

#### 6.1.4 Sequence effects on N100 amplitude in schizophrenia

Only two studies have investigated sequence effects on N100 amplitude in schizophrenia, one the published results from Study 2 of this thesis (Brown et al.,

2002) and the other, an early study on the ERP in schizophrenia (Roth & Cannon, 1972). Roth and Cannon used an auditory oddball task with an ISI of 1 second, in 21 male subjects with schizophrenia having a similar duration of illness to the chronic group used in Study 2 (mean of  $13.6 \pm 9$  years since initial hospitalisation). These researchers used rare and standard stimuli, akin to the target and non-target stimuli in terms of probability of occurrence, except that in this study the subjects were not instructed to make a response. Roth and Cannon found that N100 amplitude to *T* and *T-1* was increased, compared to *T+1* and *T+2* in the control group, but not the group with schizophrenia. In Study 2 (Chapter 5), the auditory oddball paradigm required a motor response to the target stimulus (equivalent to the rare stimuli in Roth & Cannon's paradigm), using an ISI of 1.3 seconds with both chronic and FESz groups (both male and female). This Study similarly found N100 amplitude increased to target (compared with non-target) stimuli and increased to *T-1* (compared with *T+1*) stimuli in the control group, but not in the schizophrenia group.

In summary, both the Roth and Cannon (1972) and Brown et al. (2002) studies indicate that the N100 amplitude reduction to *T+1* stimuli sequence effect, commonly found in normal controls, is not found in schizophrenia in an oddball paradigm where 'TT' occurrences do not occur. The present Study attempts to clarify whether the reduction in N100 amplitude to *T+1* is due to preparedness (probability /expectancy) or to response recovery processes.

### 6.1.5 Hypotheses:

#### *1. DR series*

There will be an increase in P300 amplitude and decrease in P300 latency and RT with repetitions in DR series (e.g. NNNNT>NNNT>NNT) in both the normal control and FESz groups.

#### *2. DA series*

P300 amplitude and latency and RT will increase with repetitions in DA series (e.g. NTNTNTT>NTNTT>NTT) in the normal group but not in the FESz group.

#### *3. Continuing (repeating) vs. discontinuing (alternating) short sequences*

P300 amplitude will be increased to discontinuing (TN, NT) compared with continuing (NN, TT) short sequences in both the normal control and FESz groups.

#### *4. N100 amplitude*

N100 amplitude to non-target  $T+1$  (TN) will be reduced compared with N100 amplitude to non-target  $T-1$  (NN).

## 6.2 METHOD

### 6.2.1 Participants

#### 6.2.1.1 Participants with FESz

Eighteen participants with FESz were recruited from community and hospital settings through the Western Sydney First Episode Psychosis Project. Of these only

the data from fourteen participants (11 males, 3 females) between 13 yrs and 23 yrs (mean = 18.5 yrs; SD = 3.1 yrs) were able to be included in the analysis. Two participants were unable to complete the paradigm, while a further two were excluded from analysis due to a high error rate in their responses to targets. FESz participants were defined as those young people presenting for the first time to health services with psychotic symptoms that warranted a diagnosis of either schizophrenia or schizophreniform disorder. Diagnosis was made by means of a consensus conference (of at least three fully qualified psychiatrists) that drew upon the interview by the participating psychiatrist, information from family and case manager and the case notes. Diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM—IV: American Psychiatric Association, 1994). Exclusion criteria were the same as for Studies 1 and 2 (Chapters 3.2.1). The majority of participants were medicated with atypical antipsychotics alone, though a small number were also receiving antidepressant or anticholinergic medications

#### 6.2.1.2 Normal control participants

Fourteen normal control participants (11 male, 3 female) between 14 yrs and 24 yrs (mean = 19.7 yrs; SD = 3.4 yrs) were recruited from the community and were gender and age matched to within 2 years with the first episode participants. Exclusion criteria were the same as for Studies 1 and 2 (see Chapter 3.2.1)

### 6.3 DATA ACQUISITION

This Study was approved by Western Sydney Area Health Service and University of Wollongong ethics' committees. Participants were seated in a reclining chair in a quiet, dimly lit laboratory, facing a video screen and wearing a pair of headphones. The paradigm used in this Study was an auditory oddball with target probability set at 0.5, 612 target (1500 Hz) tones and 612 non-target (1000 Hz) tones (with 10ms rise and fall). The tone intensity was 60 dB SPL and the fixed interstimulus interval (ISI) was 1.3 s. The design included at least 20 occurrences of each of the following sequences.

Repetition series: TT TTT TTTT TTTTT TTTTTT

Discontinuation of Repetition (*DR*) series: NT NNT NNNNT

T

Alternation series: TNT NTNT TNNT NTNTNT TNTNTNT

Discontinuation alternations (*DA*) series: NTT TNTT NTNTT TNNTT  
NTNTNTT

Participants were asked to look at a dot on the computer screen 60 cm in front of them, ignore the low non-target tones, and press two reaction time buttons with the index finger of each hand to target tones. Participants were required to respond with both hands to control for potential lateralized effects associated with unilateral motor activity. Task instructions emphasised speed and accuracy of response equally. EEGs were recorded on a DC based system (Synamps, equipped with a 16-bit A/D converter) from 19 scalp sites according to the 10-20 International system (Bloom, 1982) in reference to linked-ear electrodes with an amplification of 200 a



band pass from 0 to 50 Hz and digitised at 250 Hz. Only data recorded at Fz Cz and Pz are reported here. Horizontal EOG was recorded via electrodes placed at the outer canthus of each eye and vertical EOG was recorded via two electrodes placed 1cm above and below the midline supraorbital and infraorbital regions of the left eye. Eye correction was carried out using a technique based on Gratton, Coles & Donchin (1983). ERPs were separately sorted and averaged for each level of DR and DA as defined above under Data Acquisition (6.3)

For sub-averaged target and non-target stimuli, N100 and P300 peaks were measured relative to a pre-stimulus baseline of 200 ms by an automated system based on the detection of a consistent change in the direction of the gradient of the waveform (Haig, Gordon, Rogers & Anderson, 1995). Thus, a change from a consistently positive to a consistently negative gradient was identified as a positive peak, and vice versa for a negative peak, with the criteria that N100 occurred between 80 -140ms, and P300 occurred between 250-500 ms. Peaks thus identified were then verified through visual inspection.

## 6.4 ANALYSIS AND RESULTS

Amplitude, latency and RT measures were each subjected to ANOVA as described in greater detail below.

### 6.4.1 ERPs

In this Study ERPs were analysed in three stages:

- (i) ERPs associated with targets following one or more repetitions of the non-target (NT, NNT, ..), termed discontinuation of repetition sequences or *DR-series*
- (ii) ERPs to targets that followed an alternation sequence, termed discontinuation of alternation or *DA* series
- (iii) ERPs to targets and non-targets reflecting all 4 possibilities of the 2nd order sequence effects, namely continuing (*NN, TT*) and discontinuing sequences (*NT, TN*)

Each of these stages is discussed in order. As the P300 component was the primary interest, analyses were restricted to this component from the 3 midline sites for *DR* and *DA* sequences, and to P300 and N100 amplitudes for continuing vs. discontinuing sequences. Mean scores for N100 and P300 amplitudes at midline sites for all stages of the Study appear in a consolidated Table (See Table 6.1).

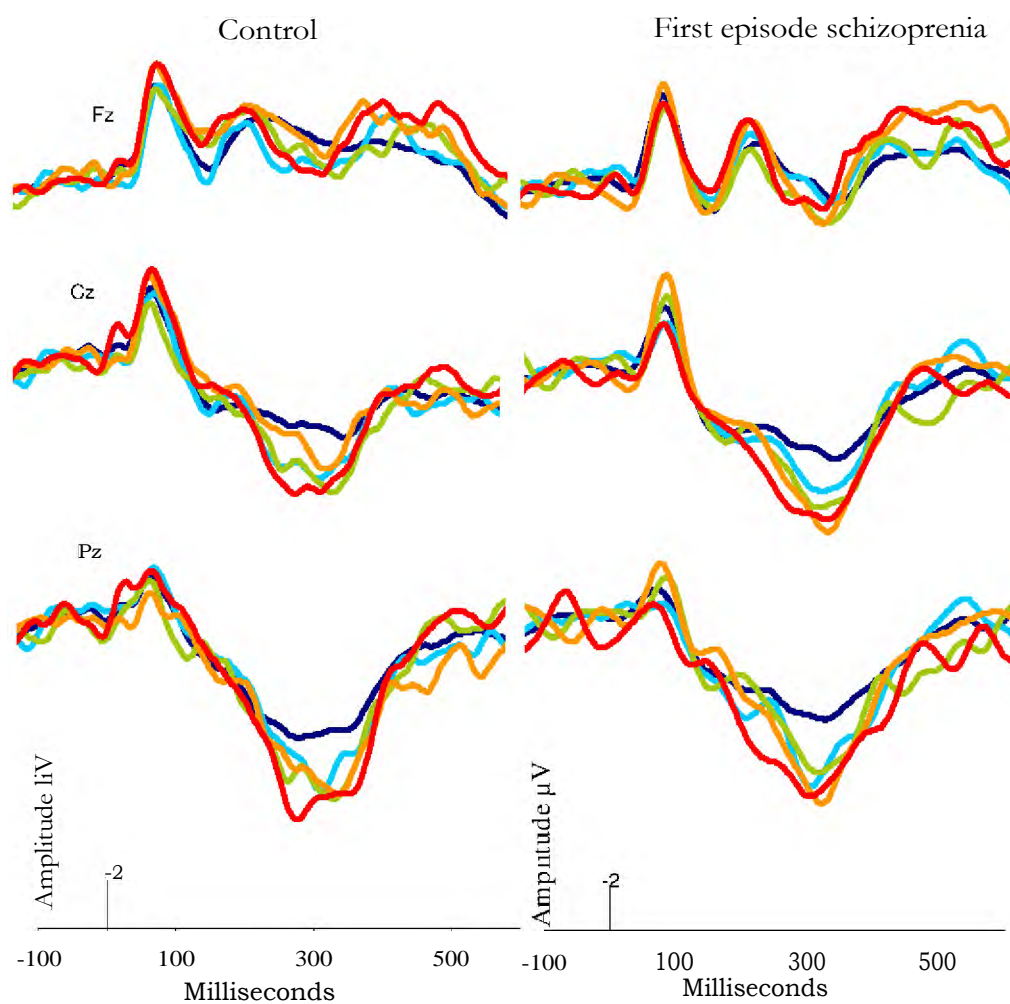
#### 6.4.1.1 Discontinuation of repetition sequence for target stimuli (DR series)

Grand average waveforms for *DR* sequences appear in Figure 6.1. P300 amplitude and latency from the *DR* series were subjected to a 2 Groups X 5 Sequences (*DR* levels) X 3 Sites (Fz, Cz, Pz) ANOVA with repeated measures on the last two factors. Linear and quadratic contrasts were examined for the sequence and site factors.

P300 amplitude: No main or interaction effects were significant for group, however, there were significant linear,  $F(1,26) = 29.4, p < 0.001$ , and quadratic,  $F(1,26) = 8.05, p < .01$ , contrasts for *DR*. P300 amplitude increased as longer strings of repetitions

were discontinued. This increase was more prominent in the first three levels, plateauing from level 3 for the control group and from level 4 for the FESz group (see Figure 6.2). There was a significant linear contrast for Site X *DR*,  $F(1.26) = 13.88$ ,  $p < 0.001$ , with sequence effects maximal at Pz.

P300 latency: There were no significant effects evident for P300 latency.



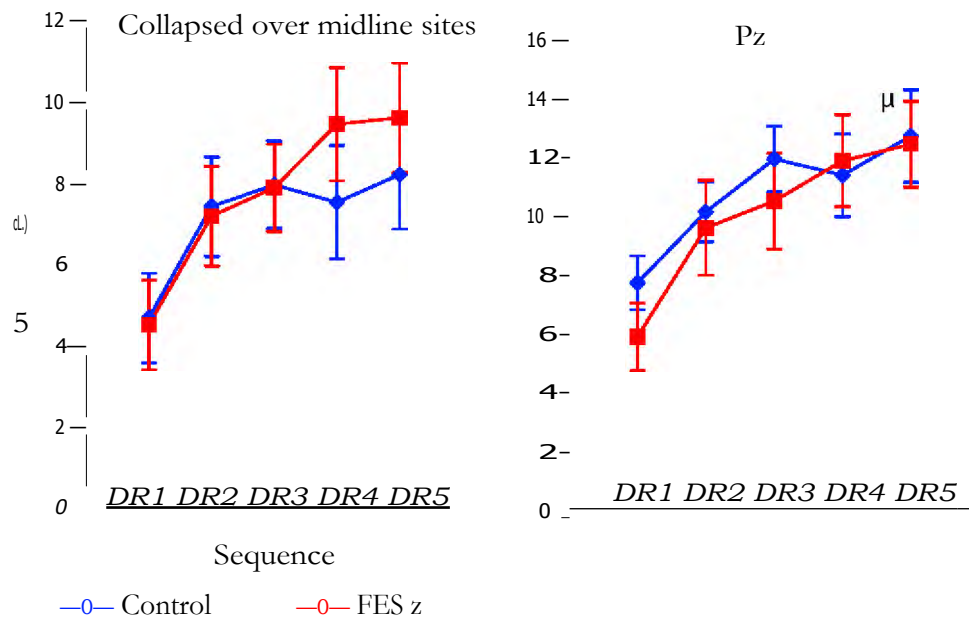


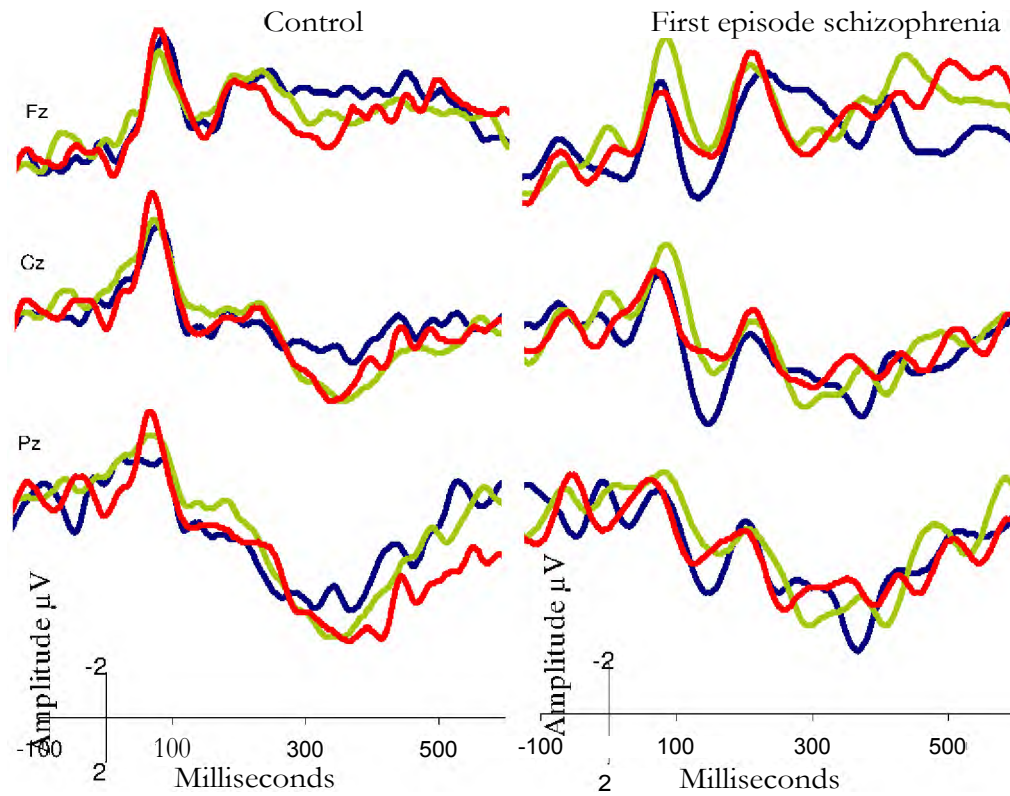
Figure 6.2 P300 amplitude across midline sites (left) and at Pz (right) for DR sequences (DR1—NT; DR2=NNT; DR3=NNNT; DR4— ; DR5—NNNNNT)

#### 6.4.1.2 Discontinuation of alternation sequence for target stimuli (*DA series*).

Grand average waveforms appear in Figure 6.3. P300 amplitude and latency from the *DA* series were subjected to a 2 Groups X 3 Sequences (*DA1*, *DA2*, *DA3*) X 3 Sites (Fz, Cz, Pz) ANOVA with repeated measures on the last two factors. Linear and quadratic contrasts were examined for sequence and site.

P300 amplitude: No main or interaction effects for group, or linear and quadratic contrasts for *DA* series were significant for P300 amplitude. There was a significant linear contrast for site,  $F(1,26) = 38.77$ ,  $p < 0.001$ , with P300 amplitude increased

from Fz to Pz. The quadratic,  $F(1,26) = 15.69$ ,  $p < .01$ , contrast arose as the increase from Fz to Cz was steeper than the increase from Cz to Pz.



effect was clearly apparent at Pz (see Figure 6.4), however, at Cz and Fz the prolongation occurred only from DA1 to DA2, giving rise to a significant DA X Site X Group quadratic, linear contrast  $F(1,26) = 11.37, p < 0.02$ .

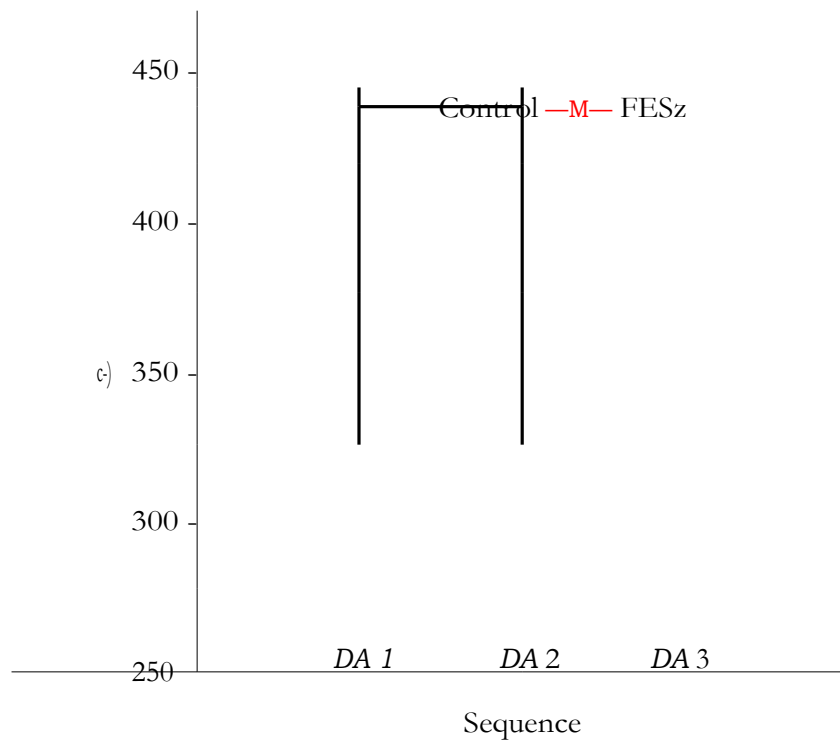


Figure 6.4 P300 latency for the two groups as a function of DA series at Pz. (DA1=NTT, DA2= NTNTT, DA3 = NTNTNTT).

#### 6.4.1.3 Continuing (NN, TT) and discontinuing (TN, NT) series.

P300 and N100 amplitudes were separately subjected to a 2 Groups X 2 Sequences (continuation & discontinuation) X 2 Stimuli (target & non-target) X 3 Sites (Fz, Cz, Pz) ANOVA with repeated measures for the last three factors.

P300 amplitude: There were no significant main or interaction effects for group. The main effect for sequence was significant,  $F(1,26) = 20.73, p < 0.001$ , with larger P300 amplitudes for discontinuing sequences, as was the main effect for Site, with a

progressively increasing P300 amplitude from frontal to central and parietal sites. The main effect for stimulus was not significant, however there were significant Sequence X Stimulus,  $F(1,26) = 5.1, p < 0.05$ , and Stimulus X Site  $F(1.4, 36.27) = 84.45, p < 0.001$ , interactions. The Sequence X Stimuli interaction arose as P300 amplitude differences between continuing vs. discontinuing sequences were more pronounced in non-target stimuli (NN vs TN) than in target stimuli (T'T vs NT). The Site X Stimuli interaction arose as P300 amplitude increased from frontal to parietal sites for target stimuli, but decreased from frontal to parietal sites for non-target stimuli (see Figure 6.6).

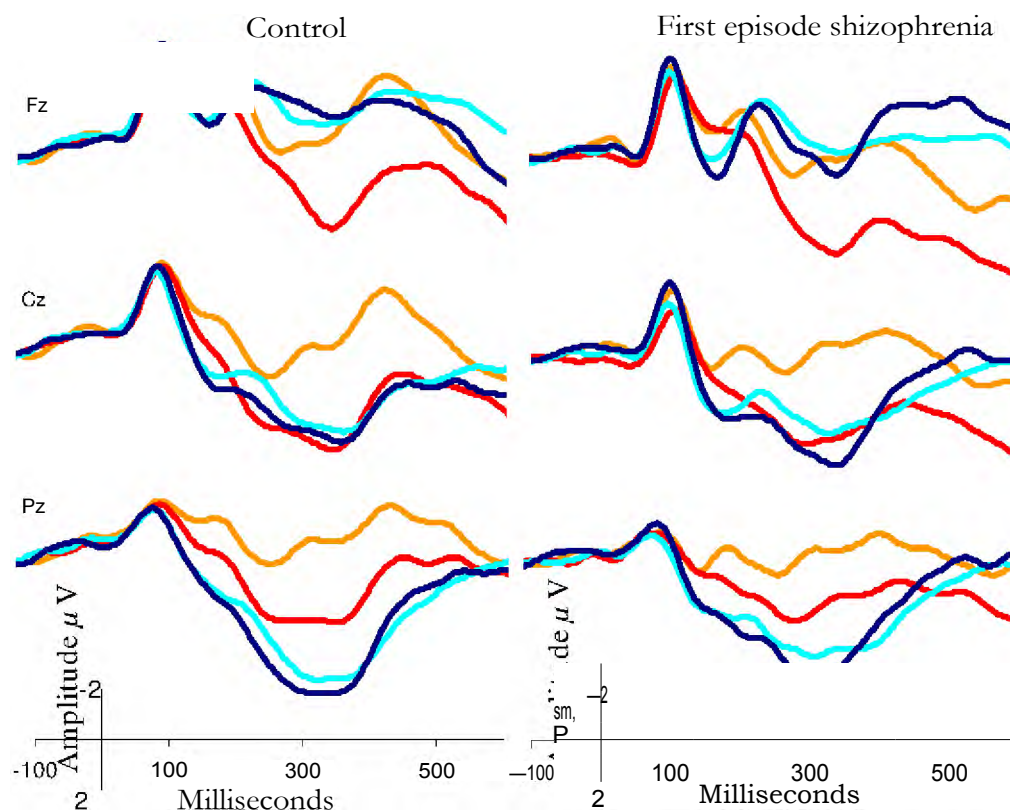


Figure 6.5 Grand average ERPs to continuing and discontinuing sequences.

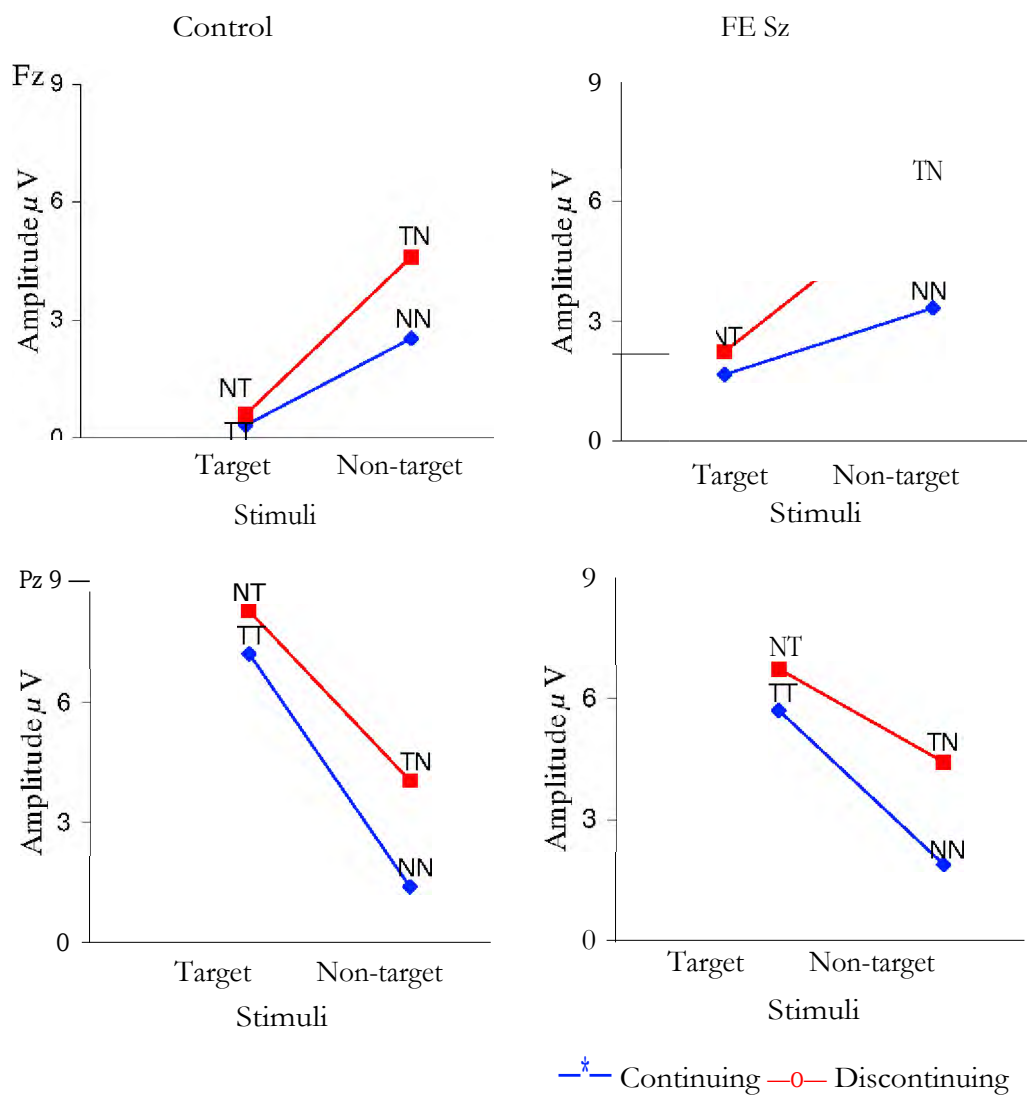


Figure 6.6 Sequence X Site and Sequence X Stimuli interactions for continuing and discontinuing sequences at Fz (top row) and Pz (bottom row) for P300 amplitude.



N100 amplitude: Mean N100 amplitudes were consistently lower for the schizophrenia group to TT, NT, NN and TN stimuli (see Table 6.1), however, the main effect for group did not reach significance  $F(1,26) = 3.06$ ,  $p = .09$ , nor were there any significant interactions with group. Main effects for stimuli or sequence were not significant, however, the Sequence X Stimuli interaction approached significance,  $F(1,26) = 3.84$ ,  $p = .06$ , as discontinuations produced increased N100 amplitude to targets but not to non-targets. No significant difference was found between N100 amplitude to NN (T-1) and TN (T+1). There was a significant main effect for site,  $F(1.34, 34.7) = 40.27$ ,  $p < 0.001$ , as N100 amplitude increased from parietal to frontal sites. There were no significant site interactions.

Table 6.1 Mean and standard deviation scores for P300 amplitude (amp) and latency (lat) and N100 components.

		Control						FESz					
		Fz		Cz		Pz		Fz		Cz		Pz	
		Mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
<i>DR1</i>	P300 amp	0.46	4.80	5.80	3.60	7.72	3.41	2.07	6.18	5.53	4.75	5.88	4.29
	P300 lat	361.61	62.75	348.63	68.59	331.47	53.00	356.35	68.36	342.86	69.36	325.79	44.04
<i>DR2</i>	P300 amp	3.24	5.24	8.06	4.78	10.13	3.81	4.06	4.56	7.83	5.36	9.59	6.02
	P300 lat	330.96	61.60	334.28	57.69	321.11	41.25	326.29	61.70	308.57	30.66	327.43	52.99
<i>DR3</i>	P300 amp	2.60	4.69	9.255	4.027	11.93	4.17	3.86	4.27	9.20	5.19	10.49	6.09
	P300lat	334.39	78.24	345.62	66.94	328.00	46.06	311.66	50.24	340.45	60.59	347.43	65.82
<i>DR4</i>	P300 amp	2.70	4.87	8.44	5.03	11.37	5.28	5.99	6.74	10.39	6.51	11.86	5.84
	P300 lat	353.90	90.25	332.09	64.08	347.93	44.91	316.32	40.53	316.32	32.33	325.41	32.61
<i>DR5</i>	P300 amp	2.46	6.27	9.38	6.02	12.70	5.88	5.32	5.66	10.96	5.16	12.43	5.44
	P300 lat	362.00	76.67	320.86	39.45	329.43	45.60	305.42	37.90	317.43	52.66	313.71	46.69
<i>DA1</i>	P300 amp	.56	5.49	5.41	4.92	7.24	5.72	4.14	6.89	7.23	4.59	8.42	5.52
	P300 lat	343.05	68.52	351.65	64.46	332.29	40.82	413.37	63.46	394.76	72.49	368.38	64.13
DA2	P300 amp	1.13	5.33	6.60	3.21	7.96	4.76	2.92	5.81	6.17	4.89	7.77	5.75
	P300 lat	378.89	65.97	384.53	68.07	358.30	54.42	331.71	60.81	376.28	65.13	376.29	65.13
DA3	P300 amp	1.39	6.32	6.44	5.59	8.76	6.44	2.64	4.72	5.92	4.26	7.28	4.39
	P300 lat	341.73	49.94	373.14	62.77	380.01	60.05	348.28	63.27	369.43	76.32	376.85	73.16
<i>TT</i>	P300 amp	0.33	4.72	5.82	4.03	7.22	3.8024	1.66	5.86	5.22	3.84	5.70	3.72
<i>NT</i>	P300 amp	0.61	4.91	6.35	3.71	8.28	3.29	2.22	5.15	6.07	4.53	6.73	4.31
<i>NN</i>	P300 amp	-2.52	6.17	3.02	5.72	1.39	3.39	3.33	5.64	2.46	3.73	1.88	1.98
<i>TN</i>	P300 amp	4.62	7.44	5.60	6.36	4.05	3.63	6.33	7.09	5.95	4.73	4.42	3.17
<i>TT</i>	N100 amp	-5.33	2.95	-4.10	2.66	-2.75	2.17	-4.44	2.50	-2.91	1.99	-1.82	1.42
<i>NT</i>	N100 amp	-6.09	2.18	-4.64	2.15	-2.93	1.97	-5.12	2.68	-3.86	2.45	-2.18	1.60
<i>NA</i>	N100 amp	-5.78	2.51	-4.71	2.52	-3.75	1.84	-4.65	2.24	-3.49	1.73	-1.76	1.37
<i>TN</i>	N100 amp	-5.72	3.04	-4.62	2.96	-3.38	2.39	-4.27	2.66	-2.70	2.01	1.85	1.05

#### 6.4.2 Response time (RT)

The mean level of accuracy was 98% for the control group and 94% for the FESz group. Only correct responses were included in the analysis. RT data was subjected to a 2 Groups X 5 Sequences (*DR* series) and a 2 Groups X 3 Sequences (*DA* series) ANOVA, with repeated measures for the *DR* and *DA* series, and linear and quadratic contrasts for the within-subjects factor.

Mean RTs were consistently lower for the FESz group (see Table 6.2), however, main effects for group did not reach significance, for *DR* or *DA* series. The larger RT variance within the FESz group (see Table 6.2.) probably contributed to this lack of significance. No significant Group X Sequence interaction was found for either *DR* or *DA* series. There were no significant linear or quadratic effects for the *DR* series, however there were significant linear,  $F(1,26) = 8.9$   $p < 0.01$ , and quadratic,  $F(1,26) = 7.6$   $p < 0.01$ , trends for the *DA* series, as RT increased (for both groups) from level 1 to 2 and then plateaued between level 2 and 3 (see Fig. 6.8.).

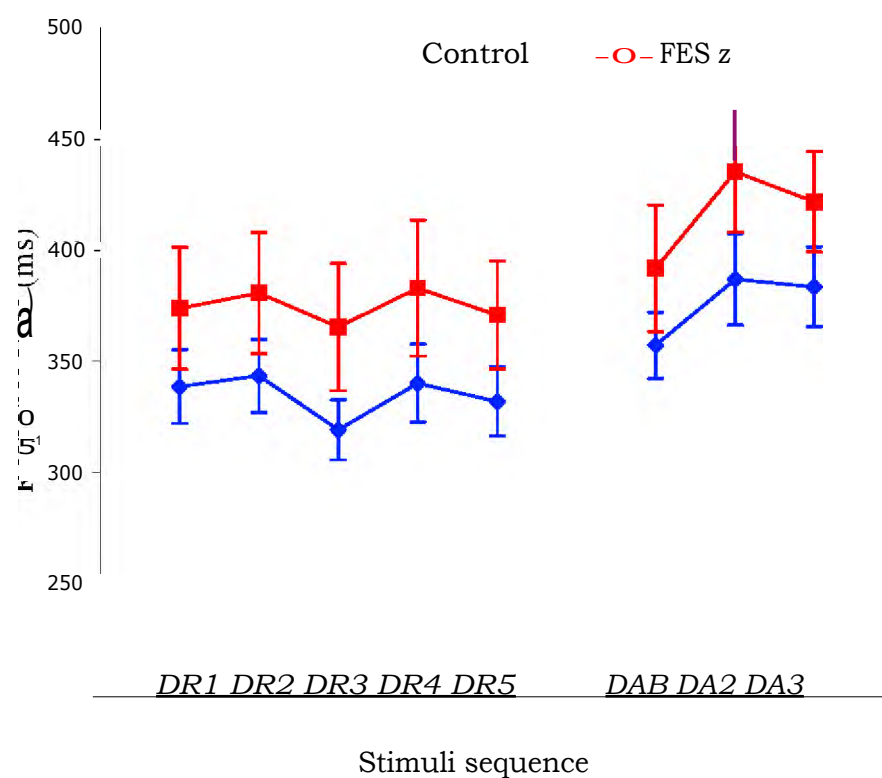


Figure 6.7 RT for DR and DA sequence levels.

Table 6.2 Mean and standard deviation values for RT.

Sequence type	Control		First episode Sz	
	Mean	SD	Mean	SD
All stimuli	339.43	53.39	370.07	89.52
DR1	338.64	61.70	373.78	102.56
DR2	343.57	61.33	380.57	102.17
DR3	319.21	50.42	365.36	106.79
DR4	340.14	65.21	382.86	114.45
DR5	331.86	57.48	370.71	91.00
DA1	357.14	55.79	391.71	106.73
DA2	386.79	76.87	435.07	101.53
DA3	383.43	67.06	421.64	84.65

## 6.5 DISCUSSION

The results from the current Study underline the relevance and importance of research on sequence effects. There has been limited research in this area in schizophrenia (see 6.1). Against the background of previous research, this Study draws attention to the fact that a large proportion of variance observed among single trials and washed out through conventional averaging of targets and non-targets (across sequence types) are due to systematic and reliable sequence effects. This Study reports results of an in-depth examination of specific sequence types that have theoretical and clinical significance. This is also the first time sequence effects on ERPs and RT have been investigated in FESz.

### 6.5.1 DR sequences

Both normal controls and the FESz group showed the same pattern of increasing P300 amplitude to *DR* series (NNNNNT> NNNNT>NNNT>NNT>NT). Previous studies in both control (Johnson & Donchin, 1980; Squires, Wickens, Squires, & Donchin, 1976) and schizophrenia groups (Duncan-Johnson & Donchin, 1982) suggested a similar trend, but results were not examined statistically and were examined over shorter sequence lengths (usually a maximum length of 4-5 stimuli). Hence, this Study confirms and extends these results by demonstrating a significant linear contrast over the *DR* series for both control and FESz groups. This result is also consistent with findings in a chronic schizophrenia group (Gonsalvez et al., 1995). P300 amplitude changes at Pz arising from *DR* sequences varied dramatically (see Figures 7.1 & 7.2), suggesting that this sequence

type has a major effect on P300 amplitude in the auditory oddball paradigm. The change in target probability (0.5 vs. 0.15), made necessary in this Study by the sequence pattern requirements, are the most likely explanation for differences in P300 amplitudes between the two groups not reaching significance. This is consistent with the results of previous studies indicating that patients with schizophrenia have significantly reduced P300 only to low probability stimuli, for example, 0.10, 0.20 and 0.30 and not to high probability stimuli, for example, 0.50 and 0.80 (Duncan, Perlstein, & Morihasa, 1987; Mathalon and Ford, 2002). The significant difference in P300 amplitude between the control and schizophrenia groups found in the Duncan-Johnson et al. sequence study, which also used a 0.50 probability, may be due to one, or a combination of variables, including task demands (simple vs. CRT), subject variables (first episode vs. chronic schizophrenia) or sequence structure (the current Study artificially increased certain types of sequences).

There were no significant *DR* series effects for P300 latency consistent with Gonsalvez et al. (1999). The lack of significant findings for *DR* series effects on RT is consistent with the observed means for *DR* series shown in the sequence tree in the Duncan-Johnson et al. (1984) study; however it is in contrast to the decrease in RT over increasing numbers of preceding non-targets found in the Gonsalvez et al. (1995) study. It seems most likely that this difference would be explained by the differences in probability in the two studies — low (0.15) in the Gonsalvez et al. study and high (0.5) in the present Study and in the Duncan-Johnson et al. study.

The absence of a *DR* effect on RT and P300 latency, alongside a significant linear effect for *DR* on P300 amplitude, adds support to the results of other studies which argue against a common expectancy-violation explanation for P300 amplitude, but is in accordance with the TTI hypothesis. Gonsalvez and associates (Croft et al., 2003; Gonsalvez et al., 1999) have argued convincingly that the consistent increase in P300 associated with increases in *DR* series is related to TTI and not to probability or number of non-target occurrences between targets. The fact that both the FESz and control groups showed similar *DR* sequence effects on P300 amplitude, would suggest that the temporal mechanisms underlying P300 variance associated with this sequence type are not impaired in this clinical group and is consistent with findings in chronic schizophrenia groups (Duncan-Johnson et al., 1984; Gonsalvez et al., 1995).

#### 6.5.2 DA sequences

An important aim of this Study was the search for an ERP index of associative strength. The results of previous studies suggested that P300 amplitude associated with DA sequences might be a useful measure. The hypothesised linear trend for increased P300 amplitude over the *DA* sequence was not found in either the control group or the group with FESz. Thus the preliminary, but promising results of previous studies were not verified when this sequence type was examined over an extended range, and with an adequate signal:noise ratio. One possible explanation for the discrepancies between results may concern the magnitude of *DA* effects. *DA* effects with increasing runs of stimuli on P300 in previous studies were quite small and not tested statistically (see

6.1.1.1.). A visual inspection of the *DA* waveforms (see Figure 6.3) for the control group in this Study shows that *DA* effects on P300s were in the expected direction for the control group, but either the magnitude of the change was too small and/or the variance too great to reach statistical significance. The magnitude of *DA* effects did not increase, as expected, with extension of the *DA* series. In any event, the unfortunate outcome of these negative results is that the *DA* effects on P300 amplitude found in this Study could not be considered a useful index of associative strength, and thus it was not possible to verify if an impairment of associative strength was central to and could contribute to the widely replicated P300 deficit observed in schizophrenia.

There was, however, as hypothesised, a significant linear *DA* series effect for controls on P300 latency, increasing with *DA* series length. As hypothesised this P300 latency increase over the *DA* series was not found in the group with FESz (see Figure 6.4). This effect has not been examined in previous research and is difficult to interpret with certainty. As these findings in the control group are in the same direction as the effects on RT, they will be discussed further after RT is examined

The hypothesised *DA* series effect on RT for controls was found, with both linear and quadratic contrasts significant. While P300 latency showed a clear increase with each *DA* level, RT showed an increase from *DA*1 to *DA*2 before plateauing between *DA*2 and *DA*3. This indicates the possibility that different mechanisms may be responsible for P300 latency and RT effects. One possible explanation is that *DA* effects on P300 latency are more stimuli-related. They may be more sensitive to the preceding stimulus patterns



and reflect more automatic, non-conscious processes and priming. In contrast, RT could be seen as more response-related and more sensitive to conscious and controlled strategies (Magliero, Bashore, Coles, & Donchin, 1984; McCarthy & Donchin, 1981; Smith, Mulder, Mulder, & Brands, 1992; Smulders, Kok, Kanemans, & Bashore, 1995; Verlager, 1997). This notion is consistent with previous investigations that have examined effects of practice (Somer et al., 1990) and manipulated expectancy (Matt et al., 1992) effects on RTs but not on ERPs. The hypothesised deficit in *DA* series effects on the schizophrenia group was not found. This finding provides further support for the hypothesis that *DA* sequence effects on P300 latency and RT may result from different mechanisms. The above suggestion would indicate that the schizophrenia group may have a deficit in automatic non-conscious mechanisms engaged by the stimulus sequence, but not in sequence effects on conscious and controlled response strategies.

### 6.5.3 Continuing (matches) vs. discontinuing (mismatches) stimuli

Both the FESz and the control groups showed increased P300 amplitude for discontinued sequence, when compared to continued sequence, for target (NT>TT) and non-target stimuli (TN>NN) in the shortened form of analysis. This is consistent with findings in healthy controls (Broderant & Polich, 1997) and in schizophrenia (Duncan-Johnson et al., 1984). However, no between-group differences emerged.

#### 6.5.4 Sequence paradigms in clinical settings:

This Study also shed light on the applicability of sequence paradigms in clinical settings. The current paradigm was more difficult for this clinical population than the shorter oddball used in Studies 1 and 2. In the previous paradigm, data from all subjects was acceptable, whereas the longer paradigm used in the current Study had a 22% attrition rate for the clinical population, but not for the normal controls. Some FESz participants were unable to finish the task, falling asleep, while a further two were excluded because of high percentage of inaccurate responses. Polich and Broderant (1997) advocate the use of sequence effects as a sensitive means for assessing implicit cognitive information-processing capabilities in applied/clinical testing situations, and have proposed the use of an abbreviated format (McCarthy, Wood, Williamson, & Spence, 1989) which would be more easily tolerated by clinical patients than traditionally extended sequence paradigms. In this Study, although employing an extended paradigm, the analysis of short continuing and discontinuing series (NN, TN, TT, NT), as proposed by Polich and Broderant was also trialled. Consistent findings for sequence types emerged over group, but no between-group differences were observed.

#### 6.5.5 T+1 vs. T-1 sequence effects on N100 amplitude

The reduced N100 amplitude for T+1 (vs T-1) found in Study 2 was not replicated in this Study. Hence, the hypothesis that this reduction in N100 amplitude could be related to post-target recovery mechanisms for the T+1 stimulus was not supported. This non-replication of reduced N100 amplitude when TT is a sequence

variant in the paradigm, is consistent with Polich and Broderant's (1997) findings and suggests an alternative explanation for the reduction in N100 to T+1, when TT is not a sequence variant in the paradigm (i.e. when every target is followed by a non-target). These findings support the possibility that mechanisms related to vigilance and preparedness may be a more likely explanation. The sequential pattern of auditory events is processed on an ongoing basis (Barry, de Pascalis, Hodder, Clarke, & Johnstone, 2003). The brain prepares for the next event, in the case of the T+1 stimulus, by reducing thresholds of activation or allocating less attention, because the non-target status of this stimulus becomes known, resulting in reduced N100 amplitude. Thus, the failure of the schizophrenia group to demonstrate a reduced N100 to T+1 stimuli appears to be associated with an ability to modulate attentional resources to predictable occurrences of irrelevant (non-target) events, a dysfunction that has been hypothesised by several information processing models (See Chapter 2.2 for details). It could also be argued that this pattern of results is not inconsistent with the Gray-Hemsley proposal that people with schizophrenia fail to establish appropriate response biases, because they are unable to use stored memories of regularities based on their previous experience. However, in the past, N100 variations have been interpreted in terms of general or more specific attentional effects and the postulation that the N100 may reflect more specific mechanisms implicated in the Gray- Hemsley model may be considered tentative. Further examination of this is feasible if, within the same subjects, deficits in latent inhibition tasks are correlated with a similar pattern of ERP deficits observed in this Study.

## 7 SPECIFICITY OF TARGET AND NON-TARGET ERP DEFICITS IN FESz COMPARED WITH CLINICAL (ADHD) AND NORMAL CONTROLS

### 7.1 INTRODUCTION AND RATIONALE

The current thesis identified several notable target and non-target ERP deficits in schizophrenia; however, it is critical to determine whether these deficits are specific to the disorder. Attention Deficit Hyperactivity Disorder (ADHD) and schizophrenia have certain cognitive deficits in common: disturbed attention (Berger & Posner 2000; Satter 1994) reduced working memory capacity (Oie, Sunde, & Rund, 1999; Karatekin & Asarnow, 1998; Ross, Harris, Olincy and Radant, 2000) and inhibitory dysfunction (Barkley 1997; Liddle & Morris, 1991). Dopamine dysfunction is also implicated in these cognitive deficits in both ADHD and schizophrenia (Nieoullon, 2002). Although ADHD is an early onset disorder, 60% of adolescents with ADHD maintain this diagnosis into adulthood (Biederman et al., 1996; Wender, 1995). Because of these shared deficits adolescents and young adults with ADHD, provide a useful psychiatric control group for exploring the specificity of ERP findings in a group with FESz. The reduced P300 amplitude observed in both these disorders makes this comparison even more compelling.

In studies investigating possible differences in the two disorders, smooth pursuit eye movement (SPEM) abnormalities (Jacobsen, Hong, Hommer et al., 1996; Ross, Olincy, Harris, Sullivan and Radant, 2000), failure to inhibit the P50 auditory ERP in a paired stimulus conditioning-testing paradigm (Olincy et al., 2000) and increased eye blinking (Jacobsen, et al., 1996), have been found to be present in schizophrenia, but not in patients with ADHD. Some studies have found that although both groups have

impaired performance on tasks measuring attention, working memory and inhibition, the pattern of deficits is different. On the continuous performance test (CPT), adult ADHD patients made more errors of omission (failure to detect the target stimulus) without increases in commission errors (incorrectly responding to a non-target) (Holdnack, Moberg Arnold, Gur, & Gur, 1995) while children with ADHD made significantly more errors of commission and omission than normal children. Patients with schizophrenia, on the other hand, have shown impaired ability to distinguish target (signal) from non-target (noise) information, as identified by the discrimination index (Cornblatt, Lenzenweger, & Erlenmeyer-Kimling, 1989). On the delayed oculomotor response task, used to study inhibitory and working memory function, both ADHD and schizophrenia patients showed disinhibition (an increased percentage of premature saccades), however, only the schizophrenia group demonstrated decreased spatial accuracy of the remembered saccade, purportedly a form of working memory (Ross et al., 2000). Some comparison studies have also reported deficits, which are sensitive, but not specific for ADHD and schizophrenia. For example, similar backward masking deficits have been found in both ADHD and schizophrenia patients (Rund, Oie, & Sundet, 1996).

Reduced P300 amplitude in the auditory oddball paradigm has been a consistent and sensitive finding for schizophrenia (see Chapter 2) and is also found in ADHD (Frank, Seiden, & Napolitano, 1998; Holcomb, Ackerman, & Dykman, 1986; Johnstone & Barry, 1996; Jonkman et al., 1997; Loiselle, Stamm, Matinsky and Whipple, 1980; Overtom et al., 1998 Robaey, Bretton, Dugas, & Renault, 1992; Satterfield, Schell, Nicholas, Satterfield and Freese, 1990). Although ERPs have been acquired in auditory

oddball paradigms for both groups, it has been difficult to compare these findings due to the difference in ages. Most schizophrenia studies have employed adults, while most studies with ADHD have employed children. Differences in paradigm variables, for example, stimuli, ISI and probability, and in data acquisition procedures, also add to the difficulty of making reliable inferences from such comparisons. The current Study has controlled for these variables, obtaining data with the same paradigm, with age and sex-matched participants with FESz, ADHD, and normal controls.

In common with trends in schizophrenia research, ADHD studies have focused on the P300 component elicited by *target stimuli*, although reduced N200 amplitude (Satterfield, Schell, Backs, & Hidaka, 1984; Satterfield et al., 1990; Satterfield, Schell, & Nicholas, 1994) and increased P200 amplitude (Holcomb et al., 1986; Satterfield et al., 1994; Robaey et al. 1992) to targets have also occasionally been reported in groups with ADHD. Findings for N100 amplitude to targets have been mixed, with some studies finding reduced N100 to targets (Loiselle et al., 1980; Satterfield et al., 1984; Satterfield et al., 1994), but not others (Johnstone & Barry, 1996; Lazzaro, Gordon, Whitmont, Meares, & Clarke, 2001). Barry, Johnstone & Clarke (2003) suggest an age-specific effect, in ADHD and control groups with N100 differentiation occurring between 7-9 years and possibly also again at 12-14 and 16-18 years.

Few studies have investigated ERPs to *non-target stimuli*. Johnstone and Barry (1996) and Winsberg, Javitt and Silipo (1997) found no significant deficits in people with ADHD with regard to N100 or P200 measures to non-target stimuli. If the N100

amplitude deficit pattern to target and non-target stimuli found in chronic and FESz groups in Study 2 is a non-specific attentional dysfunction, the ADHD group should display similar abnormalities. Given that the literature on cognitive deficits in ADHD does not suggest a failure to use context in information processing, the ADHD ERP findings discussed above, and the theoretical and empirical reasons, outlined in Chapter 4, for expecting deficits to target and non-target stimuli in schizophrenia, it was important to determine whether the N100, P200 and P300 component deficits to target and non-target stimuli ( $T-1$  &  $T+1$ ) found in Study 2 would also be present in the ADHD group.

#### 7.1.1 Hypotheses

##### a) N100 and P200 components

1. N100 amplitude will be increased to target compared with non-target stimuli in the clinical (ADHD) and normal controls, but not in the FESz group.
2. N100 amplitude will be increased to T-1 compared with T+1 stimuli in the clinical (ADHD) and normal controls, but not in the FESz group.
3. N100 latency will be delayed to non-target compared with target stimuli in the clinical (ADHD) and normal controls, but not in the FESz group.
4. P200 amplitude will be increased and prolonged to non-target compared with target stimulus in the clinical (ADHD) and normal controls, but not in the FESz group.
5. P200 amplitude will be increased and prolonged to T-1 compared with T+1 stimuli in the clinical (ADHD) and normal controls, but not in the FESz group.

b) N200 and P300 component (target stimuli)

1. N200 amplitude will be reduced in the FESz group compared to the clinical and normal controls.
2. P300 amplitude will be reduced in the FESz group compared to the clinical and normal controls.
3. P300 amplitude will be reduced in the clinical (ADHD) control group compared with the normal control group.

## 7.2 METHOD

### 7.2.1 Participants

#### Participants with ADHD

Twenty males diagnosed with ADHD aged between 13 and 26 years, with a mean age of 17 years ( $SD = 4.29$  years), were referred by paediatricians, clinical psychologists and psychiatrists to participate in this Study. All patients were subsequently interviewed using a semi-structured interview based on DSM-IV criteria for ADHD (American Psychiatric Association, 1994). All participants had been free of stimulant treatment for a period of 2 weeks or longer prior to testing. Patients with a history of neurological disorder or substance abuse were excluded from the Study.

#### Participants with FESz and normal controls

A subset of twenty male participants from the FESz group, along with their matched pairs from the normal control group, was included in this Study. The selection of



this subset from the original sample of 40 subjects used in Study 2 (see Chapter 5.2.1) was based on age matching within two years to the ADHD participants. The FESz group aged between 14 and 28 had a mean age of 18.9 years ( $SD = 2.88$  years), and the normal controls aged between 14 and 29 had a mean age of 18.45 ( $SD = 3.87$ ).

### 7.2.2 Data Acquisition and Procedure

Procedures for data acquisition were the same as Study 2 (Chapter 5.3). This Study was approved by the ethics' committees of the University of Wollongong and the Western Sydney Area Health Service.

## 7.3 ANALYSIS

### 7.3.1 Midline ERPS

N100 and P200 amplitudes and latencies were submitted separately to 3-way ANOVAs. The design incorporated 3 groups (FESz, ADHD [clinical control] and normal controls) by 3 stimuli ( $T-1$ ,  $T$ ,  $T+1$ ) by 3 electrode sites (Fz, Cz, Pz), with repeated measures for site and stimulus factors. For the group factor, two specific contrasts were conducted: (i) FESz vs. ADHD and normal controls, to determine if the FESz group was different from the 2 control groups, and (ii) ADHD vs. normal controls to determine if the clinical control group differed from the normal control group. For the stimulus factor, two specific planned contrasts were carried out: (i) target vs. non-targets ( $T$  vs.  $T-1/T+1$ ) to examine whether the target status influenced ERP components and (ii) between non-targets ( $T-1$  vs.  $T+1$ ) to examine whether the sequential position of the non-target

affected ERP components. For the site factor, linear and quadratic contrasts were examined, the linear contrast purporting to examine reduced amplitudes at parietal sites (Fz vs Pz) and the quadratic contrast purporting to test the frequently observed maximal amplitudes at central sites (Cz vs. Fz+Pz).

N200 and P300 components were reliably observed only to the target stimulus and were therefore subjected to a group (FESz, ADHD, normal controls) by site (Fz, Cz, Pz) ANOVA repeated measures design. Similar linear and quadratic contrasts as described above were conducted for the site factor. The Statistical Package for Social Sciences 10.0 program (SPSS Inc., 1999) was used in all analyses.

As a result of the above contrasts all comparisons were based on a single degree of freedom, obviating the need to employ statistical procedures to correct for alpha (e.g. Bonferroni) or sphericity effects (e.g., Greenhouse-Geisser).

### 7.3.2 Discriminant function analysis

The purpose of conducting a discriminant function (DA) analysis was to determine the accuracy with which the ERP measures could correctly classify persons with and without schizophrenia. Hence two groups were defined: the schizophrenia group and the non-schizophrenia group (the two control groups combined). Component amplitude and latency measures on which the clinical and control groups were

significantly different in ANOVA results were entered into three separate stepwise discriminant function analyses in the following manner:

1. N100 and P200 component amplitude and latency for target, T-1 and T+1 stimuli. Where the number of significant differences exceeded the number of variables permissible under subject-to-variable ratio recommendations, and differences were observed at more than one site, then only the site at which the component has maximal between stimuli differences for amplitude/latency was entered (E.g., Cz for P200).
2. All significant target N200 and P300 amplitude and latency at midline sites.
3. Variables chosen from the stepwise Dfas described in 1 and 2 were then entered into a third stepwise Dfa

## 7.4 RESULTS

The same ERP waveforms are presented in Figure 7.1 to accentuate between-group differences and in Figure 7.2 to accentuate within group differences. Mean and standard deviation amplitude and latency values are presented in Tables 7.1 and 7.2 respectively. A small percentage (2% for controls and 3% for FESz and ADHD) of ERP measures were identified as outliers (greater or less than one and a half the interquartile

range from the upper and lower quartile). All results below are based on data with outliers; however results remained significant following removal of outliers. All significant results appear in Tables 7.2 — 7.4 or are reported in text. Statistical values for non-significant results are not reported, but are attached (see Appendix 3, CD-Rom).

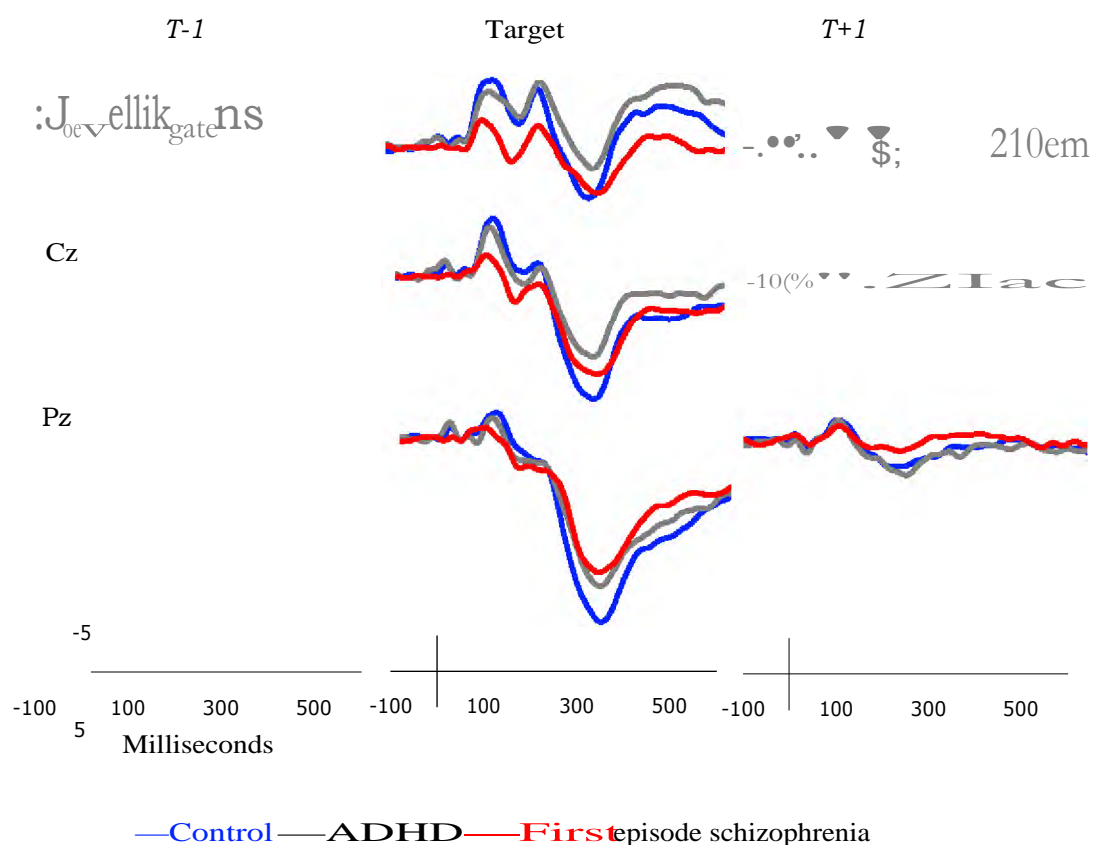


Figure 7.1 ERPs to T-1, Target and T+1 stimulus for normal control, ADHD and FESz groups

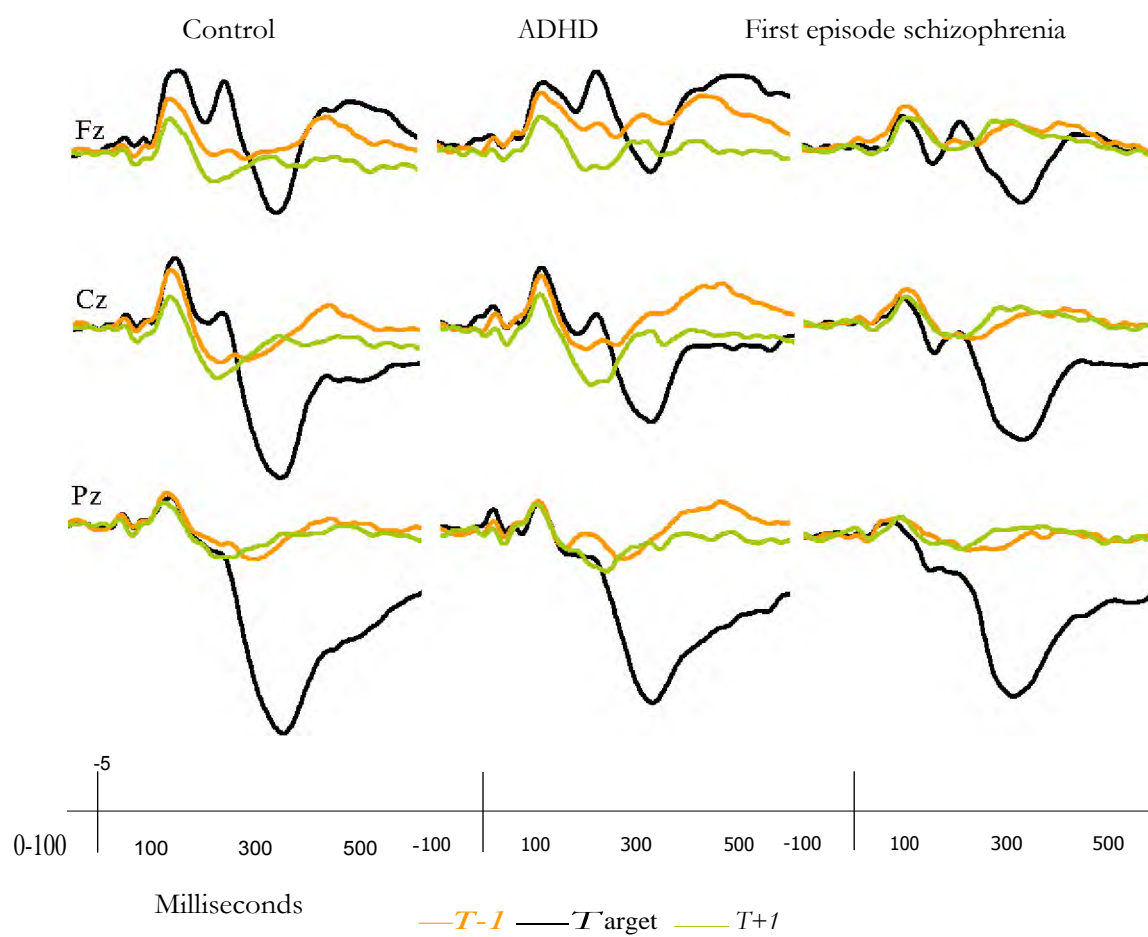


Figure 7.2 ERP waveforms to T-1, Target and T+1 stimuli, superimposed to show within group differences, for control ADHD and FESz.

Table 7.1 N100 and P200 mean and standard deviation amplitude and latency scores

		FESz		Normal control		ADHD	
		Mean	SD	Mean	SD	Mean	SD
T-1							
N100 amplitude	Fz	-6.05	2.73	-7.39	4.21	-7.74	4.69
	Cz	-5.14	2.41	-7.87	4.61	-6.48	4.72
	Pz	-3.79	2.21	-5.42	3.28	-4.08	2.11
N100 latency	Fz	108.53	22.66	110.76	19.56	111.40	14.64
	Cz	103.74	21.99	105.48	13.57	99.60	10.37
	Pz	96.29	18.99	98.92	16.14	96.60	10.96
P200 amplitude	Fz	1.51	3.82	2.29	4.24	0.15	4.06
	Cz	4.07	3.89	5.70	4.98	4.97	4.09
	Pz	2.96	3.41	3.88	3.93	3.89	3.08
P200 latency	Fz	196.17	35.54	182.97	27.81	188.67	34.22
	Cz	199.03	32.99	178.57	25.28	183.71	32.00
	Pz	200.54	38.57	184.35	33.14	176.46	35.44
Tar get							
N100 amplitude	Fz	-4.95	3.55	-10.93	4.56	-9.66	5.56
	Cz	-4.47	2.34	-9.47	5.33	-8.29	6.55
	Pz	-3.22	2.02	-4.88	3.34	-4.46	2.96
N100 latency	Fz	107.56	18.39	114.50	16.07	117.17	18.87
	Cz	95.31	18.04	106.28	11.52	103.96	17.23
	Pz	92.87	19.66	96.39	19.65	91.00	18.62
P200 amplitude	Fz	3.02	5.98	-1.66	5.31	-2.86	5.05
	Cz	4.33	5.37	1.63	7.57	2.98	6.08
	Pz	5.16	4.51	3.08	6.33	4.45	3.82
P200 latency	Fz	168.32	15.54	176.14	16.31	172.13	16.57
	Cz	161.55	17.38	171.56	17.47	170.05	19.83
	Pz	156.11	22.97	156.00	28.94	161.36	24.26
N100 amplitude	Fz	-5.36	2.97	-4.74	3.74	-5.23	3.69
	Cz	-3.91	2.38	-5.05	4.35	-4.82	4.66
	Pz	-3.23	2.51	-4.33	4.04	-4.03	3.73
N100 latency	Fz	122.07	39.49	107.02	14.34	110.45	16.47
	Cz	104.27	16.06	101.66	14.86	95.88	12.20
	Pz	92.99	16.18	97.00	14.62	94.80	12.59
P200 amplitude	Fz	1.64	3.57	4.62	4.11	4.02	5.44
	Cz	3.26	3.61	6.97	4.42	7.52	4.28
	Pz	2.57	3.35	4.83	3.40	6.11	3.00
P200 latency	Fz	185.55	26.80	184.98	21.00	197.24	22.04
	Cz	180.28	28.73	185.40	20.77	198.39	24.15
	Pz	163.23	33.65	190.80	21.41	202.69	26.08

Table 7.2 N100 and P200 mean and standard deviation amplitude and latency scores

		FESz		Normal control		ADHD	
		Mean	SD	Mean	SD	Mean	SD
N200 amplitude	Fz	-5.4408	5.1813	-10.496	6.81705	-10.605	6.95912
	Cz	-0.4826	6.30042	-3.8156	9.12753	-2.5057	7.90954
	Pz	1.28895	4.70631	0.66085	6.37969	1.78905	5.93713
N200 latency	Fz	222.659	21.9944	217.299	20.9499	216.96	17.5089
	Cz	214.915	18.7223	211.082	13.3428	215.091	18.3824
	Pz	203.918	34.9195	194.642	26.1287	202.477	23.742
P300 amplitude	Fz	9.82375	8.60497	9.8305	7.93304	4.0376	7.64664
	Cz	16.4389	8.86339	20.3025	9.87283	11.9716	9.54835
	Pz	20.8744	9.67486	27.8976	10.4392	19.969	9.93474
P300 latency	Fz	325.466	54.8732	320.179	29.1231	318.784	22.2235
	Cz	322.769	40.9583	317.4	29.4018	309.208	47.9957
	Pz	327.576	40.7367	325.393	24.945	316.51	40.3415

#### 7.4.1 N100 Component

##### 7.4.1.1 Amplitude

The results of the statistical analyses are summarised in Table 7.3

FESz versus clinical (ADHD) and normal controls

There was a significant main effect for group, with N100 amplitude reduced in the FESz group compared with the clinical (ADHD) and normal control groups. This main effect for group was further qualified by Group X Stimulus, Group X Site and Group X Stimulus X Site interactions as follows (see Table 7.3, values in blue & Figure 7.3). With regard to the target vs. non-target comparisons, significant group differences were observed at frontal rather than parietal sites, so that the control and ADHD groups demonstrated reduced N100 amplitude to the non-target compared with target stimuli, while the FESz group demonstrated similarly reduced amplitudes to all stimuli. Additionally the ADHD and normal control group appeared to have reduced amplitude to T+1 compared with T-1, at the frontal rather than parietal sites, with the results approaching significance ( $p = .06$ ), whereas the FESz group had similarly reduced amplitudes for both non-targets (see Figure 7.3). Hence, the reduction in N100 amplitude in the FESz group compared with normal and clinical controls was most prominent to target compared with non-target stimuli.

Over group and site, targets produced larger amplitudes than non-targets and T+1 produced larger amplitudes than T-1, with this effect being pronounced at the fronto-



central rather than parietal sites (see Table 7.3, values in green & Figure 7.3). As mentioned above, this effect was qualified by a group interaction with the results of the ADHD and normal control groups (but not the FESz group) contributing to these effects.

The expected fronto-central maximum for N100 amplitude was also observed, with both linear and quadratic contrasts for site yielding significant results (see Table 7.3, values in red).

Table 7.3 Summary of N100 Amplitude results

			FESz vs ADHD+NC 41(1,58)		ADHD vs NC <i>df</i> (1,38)	
	Stimulus	Site	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Group			5.91	.02		
Grp X Stim	T vs NTs		9.96	.003		
	T-1 vs T+1					
Grp X Site		Cz vs Fz & Pz	4.33	.04		
		Fz vs Pz				
Grp X Stim X Site	T vs NTs	Cz vs Fz & Pz	18.47	.000		
		Fz vs Pz				
	T-1 vs T+1	Cz vs Fz & Pz	—			
		Fz vs Pz	3.46	.06		
Stimulus	T vs NTs		5.31	.03	19.76	.0001
	T-1 vs T+1		13.07	.001	16.19	.0001
Stim X Site	T vs NTs	Cz vs Fz & Pz				
		Fz vs Pz			51.22	.0001
	T-1 vs T+1	Cz vs Fz & Pz	6.02	.02	4.76	.04
		Fz vs Pz	4.54	.04	9.80	.003
Site		Cz vs Fz & Pz	5.88	.02	10.85	.002
		Fz vs Pz	45.77	.0001	44.90	.0001

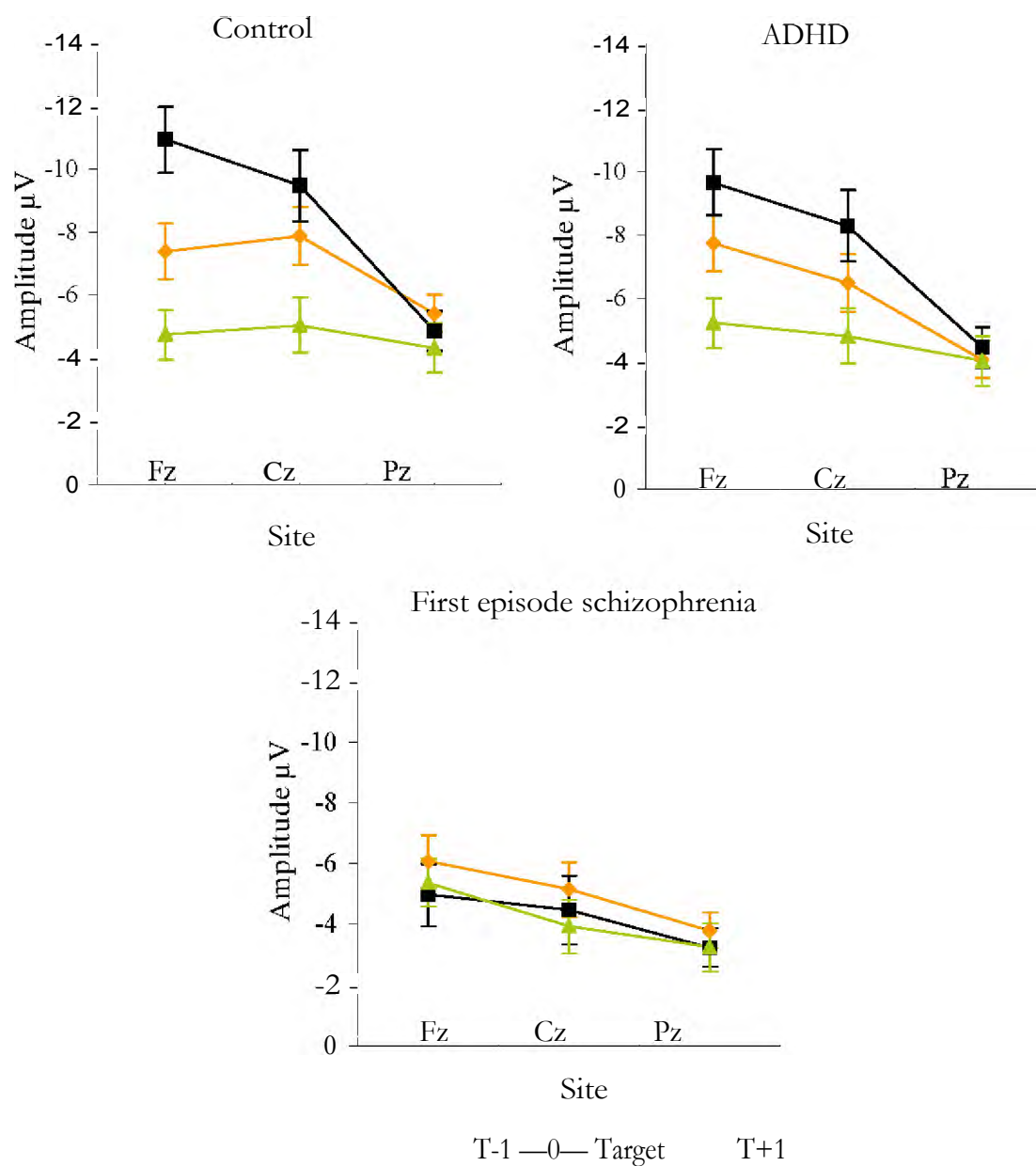


Figure 7.3 N100 amplitude to target and non-target stimuli for all groups.

### Clinical (ADHD) versus normal controls

Neither main effects for group nor interaction effects were significant. Over group and site, targets produced larger amplitudes than non-targets and T+1 produced larger amplitudes than T-1, with this effect being pronounced at the fronto-central rather than parietal sites (see Table 7.3, values in green & Figure 7.3). This effect was qualified by a Stimulus X Site interaction with the target vs. non-target effect occurring at frontal compared with parietal sites, and the non-target effect, showing both linear and quadratic contrasts, being maximal at fronto-central compared with parietal sites.

The expected fronto-central maximum for N100 amplitude was also observed, with both linear and quadratic contrasts for site yielding significant results (see Table 7.3, values in red).

Summary: The results yielded an interesting pattern of deficits that appear to be specific to schizophrenia. Specifically, the FESz group did not differ in the way they responded between targets and non-targets, or between the two non-targets, while the normal control and ADHD groups demonstrated decreased N100 amplitude to non-targets compared with targets (maximal at fronto-central sites) and decreased N100 amplitude to T+1 compared with T-1 (maximal at fronto-central sites).

#### 7.4.1.2 Latency

##### FESz versus clinical (ADHD) and normal controls

N100 latency effects were not significant for group, however, there was a significant Group X Stimulus interaction for the target vs. non-target contrast,  $F(1,58) = 5.63$ ,  $p < 0.05$ , as non-targets produced more prolonged latencies than targets in the clinical (ADHD) and normal control group, while the FESz group showed the opposite pattern. As a result, compared with the control groups, the FESz group showed delayed latency to target rather than non-target stimuli.

Over groups there was a significant linear contrast for site,  $F(1,58) = 55.49$ ,  $p < 0.001$ , with N100 latency prolonged at frontal compared with parietal sites.

##### Clinical controls (ADHD) versus normal control

Effects were not significant for group or interactions with group for the ADHD vs. normal controls comparison. There was a Stimuli X Site interaction for the target vs. non-target comparison,  $F(1,38) = 4.41$ ,  $p < 0.05$ , indicating prolonged N100 latency to target compared with non-target stimuli at frontal, rather than parietal sites. There was a main effect for site, with the significant linear contrast,  $F(1,38) = 50.4$ ,  $p < 0.001$ , showing N100 latency prolonged at frontal compared with parietal sites.

Summary: Targets (vs. non-targets) produced a delayed N100 in the FESz group, but had the opposite effect for the two control groups who responded similarly, suggesting that this latency effect might be specific to schizophrenia.

#### 7.4.2 P200 component

##### 7.4.2.1 Amplitude

The results of the statistical analyses are summarised in Table 7.4

FESz versus clinical (ADHD) and normal controls

Main effects for group were not significant, although Group X Stimuli, Group X Site and Group X Stimuli X Site interactions were significant. With regard to the target vs. non-target comparisons, the control and ADHD groups demonstrated reduced P200 amplitude to the target compared with non-target stimuli, especially at the frontal site (vs. parietal) while the FESz group had similar amplitudes to both stimuli types (see Table 7.4, values in blue & Figures 7.4 and 7.5). Additionally the ADHD and normal control group showed enhanced amplitude to T+1 (vs. T-1) across sites, whereas the FESz group did not differ in the way that they responded to the two non-targets (see Table 7.4, values in blue & Figure 7.4).

Over the three groups, the Stimulus X Site interactions (linear and quadratic) for the target vs. non-target comparison were significant, suggesting stimuli-based topographical shifts, with targets producing maximal amplitude parietally and non-

targets centrally (see Table 7.4, values in green & Figure 7.5). For the non-target comparison, a quadratic contrast indicated the reduced P200 amplitude to T-1 compared with T+1 stimulus was maximal at the vertex (see Table 7.4, values in green).

Across groups and stimuli, the expected centro-parietal maximum for P200 amplitude was also observed, with both linear and quadratic contrasts yielding significant results (see Table 7.4, values in red).

Table 7.4 Summary of P200 amplitude results

		<i>FESz vs ADHD+NC</i>		<i>ADHD vs NC</i>	
		df(1,58)		df(1,38)	
Group	Stimulus	Site			
Grp X Stim	T vs NTs		11.18	.001	
	T-1 vs T+1		5.71	.02	
Grp X Site		Cz vs Fz & Pz	5.57	.02	
		Fz vs Pz			
Grp X Stim X Site	T vs NTs	Cz vs Fz & Pz			
		Fz vs Pz	4.30	.04	
	T-1 vs T+1	Cz vs Fz & Pz			
		Fz vs Pz			
Stimulus	T vs NTs			14.44	.001
	T-1 vs T+1			14.23	.001
Stimulus X Site	T vs NTs	Cz vs Fz & Pz	5.96	.02	
		Fz vs Pz	11.08	.002	27.05 .0001
	T-1 vs T+1	Cz vs Fz & Pz	3.98	.05	
		Fz vs Pz		4.62	0.04
Site		Cz vs Fz & Pz	45.71	.0001	51.64 .0001
		Fz vs Pz	24.36	.0001	26.62 .0001

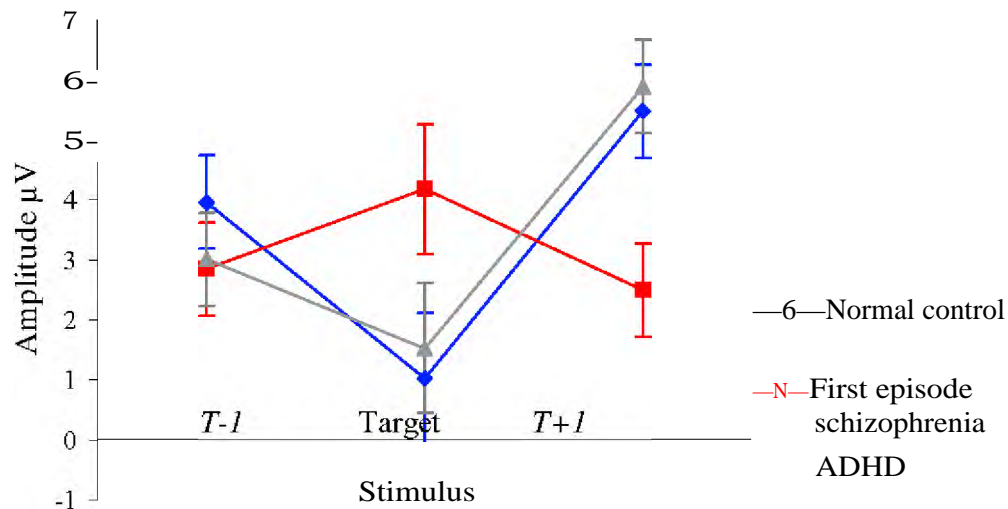


Figure 7.4 P200 amplitude to target and non-target stimuli for all groups across midline sites.

#### Clinical control (ADHD) versus normal control

Effects were not significant for group nor were any interaction effects significant with group for the ADHD vs. normal controls comparison.

Over groups, there was a significant main effect for stimulus for both the target vs. non-target contrast and the non-target contrast, T-1 vs. T+1, with target stimuli producing reduced amplitude compared with the non-target stimuli and T-1 producing reduced amplitude compared with T+1. Across groups, the expected centro-parietal maximum for P200 amplitude was also observed, with both linear and quadratic contrasts yielding significant results.

Summary: The reduced P200 amplitude found frontally, to target compared with non-target stimuli, which was present in the ADHD and normal controls, was not found in the FESz group. Hence, these P200 amplitude deficits also appear to be specific to FESz.

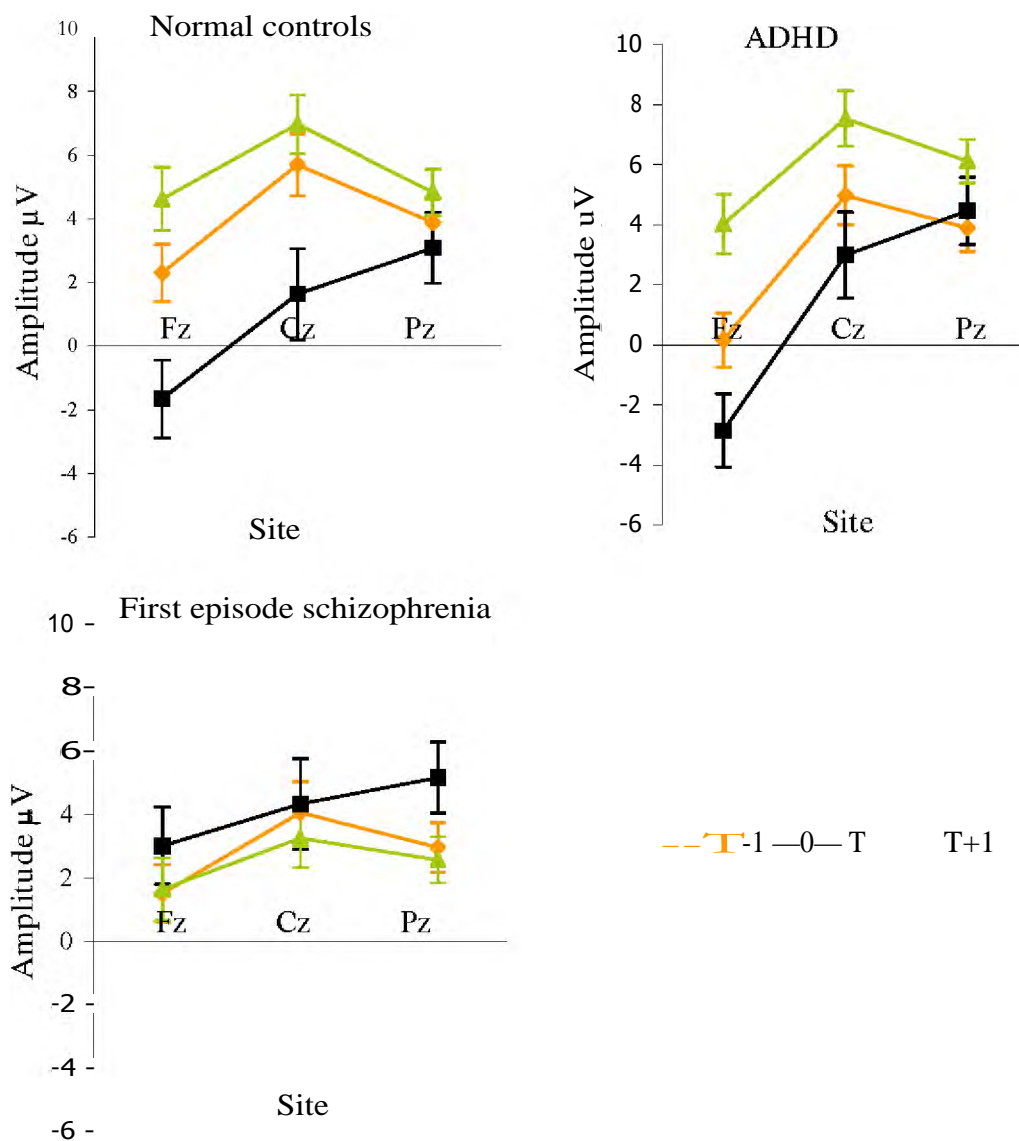


Figure 7.5 P200 amplitude to target and non-target stimuli (T-1 & T+1) for all groups.



#### 7.4.2.2 Latency

The results of the statistical analyses are summarised in Table 7.5.

##### FESz versus clinical (ADHD) and normal controls

Effects were not significant for group, however, Group X Stimulus and Group X Stimulus X Site interactions were significant as follows. With regard to the non-target comparisons, significant group differences were observed at parietal rather than frontal sites, so that the control and ADHD groups demonstrated earlier P200 latency to T-1 compared with T+1 stimuli, while the FESz group showed the reverse pattern (see Table 7.5 values, in blue & mean scores in Table 7.1).

Across group, latency was earlier to targets than non-targets and this effect was maximal at Pz (see Table 7.5, values in green & mean scores in Table 7.1). The main effect for site was also significant; the significant linear contrast indicated latency was earliest at Pz.

##### Clinical control (ADHD) versus normal control

Effects were not significant for group nor were any interaction effects significant with group for the ADHD vs. normal controls comparison.

Over group, there was a significant main effect for stimulus for both the target vs. non-target contrast and the non-target contrast, T-1 vs.T+1, with target stimuli producing

earlier latency compared with the non-target stimuli and T-1 producing earlier latency' compared with T+1.

Table 7.5 Summary of P200 latency results

		FESz vs ADHD+NC		ADHD vs NC	
		<i>df</i> (1,58)		<i>df</i> (1,38)	
	Stimulus	Site	<i>F</i>	<i>p</i>	
Group					
Grp X Stim	T vs NTs				
	T-1 vs T+1		16.13	.001	
Grp X Site		Cz vs Fz & Pz			
		Fz vs Pz			
Grp X Stim X T vs NTs		Cz vs Fz & Pz			
Site		Fz vs Pz			
	T-1 vs T+1	Cz vs Fz & Pz			
		Fz vs Pz	11.32	.001	
Stimulus	T vs NTs		53.17	.0001	33.70 .0001
	T-1 vs T+1				5.20 .03
Stim X Site	T vs NTs	Cz vs Fz & Pz			
		Fz vs Pz			6.68 .01
	T-1 vs T+1	Cz vs Fz & Pz			
		Fz vs Pz			4.52 .04
Site		Cz vs Fz & Pz			
		Fz vs Pz	9.61	.003	4.09 .056

This effect for both contrasts was qualified by an interaction with site, indicating that the difference was maximal parietally (see Table 7.5, values in green). Across group, the expected centro-parietal maximum for P200 amplitude was also observed, with both linear and quadratic contrasts yielding significant results (see Table 7.5, red).

Summary: T+1 stimuli produced delayed latency in the two control groups, but not in the FESz group, an effect maximal at the parietal site.

### 7.4.3 N200 component

#### 7.4.3.1 Amplitude

FESz versus clinical (ADHD) and normal controls

Main Effects were not significant for group. However, there was a Group X Site interaction with a significant linear contrast,  $F(1,58) = 6.94$ ,  $p = 0.01$ , indicating that the FESz showed reduced frontal N200 amplitude compared with normal and clinical (ADHD) controls. Significant linear,  $F(1,58) = 95.01$ ,  $p < .0001$ , and quadratic,  $F(1,58) = 7.94$ ,  $p < .01$ , contrasts for site indicated that N200 amplitude was maximal frontally with marked reductions at centro-parietal sites.

Clinical control (ADHD) versus normal control

Effects were not significant for group or group X site interaction. Significant linear,  $F(1,38) = 99.64$ ,  $p < 0.001$ , and quadratic,  $F(1,38) = 4.97$ ,  $p < .05$ , contrasts for site indicated that N200 amplitude was maximal frontally.

Summary: There was a frontal reduction in N200 amplitude specific to the FESz group.

#### 7.4.3.2 Latency

FESz versus clinical (ADHD) and normal controls

Effects were not significant for group or Group X Site interaction. Significant linear,  $F(1,58) = 24.91$ ,  $p < 0.001$ , and quadratic,  $F(1,58) = 4.36$   $p < .05$ , contrasts for site indicated that N200 latency was prolonged fronto-centrally.

Clinical control (ADHD) versus normal control

Effects were not significant for group or Group X Site interaction. Significant linear,  $F(1,58) = 25.13$ ,  $p < 0.001$ , and quadratic,  $F(1,58) = 9.58$   $p < .01$ , contrasts for site indicated that N200 latency was prolonged fronto-centrally.

#### 7.4.4 P300 component

##### 7.4.4.1 Amplitude

FESz versus clinical (ADHD) and normal controls

The main effect for group was not significant, however, there was a main effect for site, with the expected parietal maximum for P300 amplitude being observed for the linear contrast,  $F(1,58) = 138.53$ ,  $p < .001$ . This result was qualified by a significant Group X Site interaction with the linear contrast,  $F(1,58) = 6.23$ ,  $p < 0.01$ , indicating that this pattern was maximal for the control (clinical + ADHD) group compared with the FESz group (see Figure 7.6).

### Clinical (ADHD) versus normal controls

There was a significant main effect for group,  $F(1,38) = 7.88$ ,  $p < .01$  with P300 amplitude reduced in the ADHD group compared with normal controls (see Figure 7.6). Across group, the expected parietal maximum for P300 amplitude was also observed, with a significant linear contrast,  $F(1,38) = 145.57$ ,  $p < .001$ , for site.

Summary: Over sites, the ADHD group demonstrated reduced P300 amplitude compared with normal controls. The FESz group did not demonstrate a significantly reduced P300 amplitude when compared to the combined (clinical + normal ) control group. The conventionally observed enhancement of P300 amplitude from frontal to parietal sites was more pronounced for the combined control groups when compared with the FESz group.

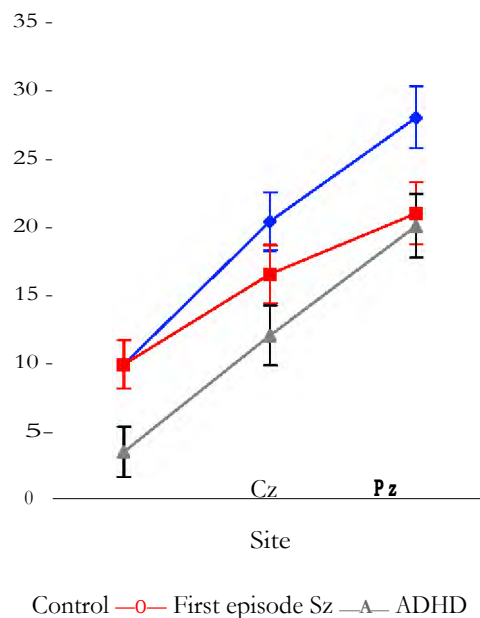


Figure 7.6 P300 amplitude for all groups at midline sites.

#### 7.4.4.2 Latency

Effects for group, site and group by site interactions were not significant for P300 latency in either of the group comparisons.

#### 7.4.5 Discriminant function analysis (DA)

The results of the three stepwise DAs are presented in Table 7.6

Table 7.6 Results of stepwise discriminant function analyses

% Correctly classified			
Variables entered in stepwise DA	FESz	ADHD and normal controls	Variables included by stepwise DA *
1. N100, P200 T, T-1, T+1	85% Wilk's 43,58) = .555, $\chi^2 = 33.28$ , $p < .001$	82.5%	T+1 P200 latency (-0.71) T-1 P200 latency (0.43) T N100 amplitude (.67)
2. N200, P300 T	65% Wilk's 41,58) = .869, $\chi^2 = 8.06$ , $p < .01$	55%	T N200 amplitude (1.0)
3. Combined stepwise variables from 1 and 2	85% Wilk's 43,58) = .555, $\chi^2 = 33.28$ , $p < .001$	82.5%	T+1 P200 latency (-0.71) T-1 P200 latency (0.43) T N100 amplitude (.67)

\* standardised canonical discriminant function co-efficients in brackets

Entering the same target and non-target N100 and P200 components as those used in the DA in Study 2 (see 7.3.2) 17.5% of the clinical + normal control group, i.e. three normal controls and four ADHD controls, would have been incorrectly classified as belonging to the schizophrenia group (false positives), while 15%, 3 people with FESz, would have been inaccurately identified as belonging to the clinical and normal control group (false negatives). However, when only N200 and P300 components to target stimuli were used, the accuracy rate was dramatically reduced with 45% of the clinical + normal control group, (10 normal controls & 8 ADHD controls) being incorrectly classified.

When the critical variables selected by the two stepwise analyses (i. N100, P200 & ii. N200, P300) above were combined and entered into a stepwise DA the results were identical to the N100, P200 analysis. In other words, the later components (N200, P300) derived from the target stimuli failed to enhance the classification accuracy derived from the earlier components (N100, P200).

## 7.5 DISCUSSION

The results yielded several distinctive findings for both N100 and P200 amplitude and latency for the FESz group, compared to the clinical (ADHD) and normal control group, supporting the possibility that these results are specific to schizophrenia. In

contrast, reduced P300 amplitude was not found to be specific for the FESz group and also occurred in ADHD.

Results supported the hypothesis that the pattern of N100 and P200 deficits found in schizophrenia compared with normal controls would not be found in the ADHD group. The ADHD patients showed a similar pattern of N100 amplitude differences as the normal controls for both the target vs. non-target comparison, with non-targets producing decreased N100 amplitude compared with targets. In addition, for the non-target, T-1 vs. T+1 comparison, T+1 produced reduced N100 amplitude compared with T-1 for both control groups. The patients with FESz, however, did not show this N100 amplitude differentiation, either between target and non-target stimuli, or between non-target, T-1 and T+1, stimuli. N100 amplitude was reduced overall in the FESz group compared to the control and ADHD group.

This difference in N100 amplitude findings between the first episode and ADHD groups would seem to indicate that the N100 amplitude deficits in FESz are not simply the result of non-specific attentional deficits, as one would expect to find the pattern of deficits in the ADHD group if this was so. The results of Study 3 (Chapter 6) suggest that the lack of differentiation between T-1 and T+1 stimulus in FESz is not simply the result of a disturbed recovery following the response to the target stimulus. Additionally, Study 3 indicated that normal controls no longer produce differentiated N100 amplitude to T-1 and T+1 stimuli, when T+1 stimuli are not predictable. In combination, these results suggest that the FESz group were not able to make use of past regularities, i.e. a target



will always be followed by a non-target to establish appropriate response biases, i.e. reduced allocation of attention to T+1 stimuli reflected in a reduction in N100 amplitude. The results could also suggest a heightened state that allows even predictable irrelevant stimuli, such as T+1, to capture attentional resources.

Similarly, for P200 amplitude, the ADHD and normal control groups showed a differentiation between stimuli, with a P200 amplitude reduction to target, compared to non-target stimuli. This pattern was not found in the FESz group, as target stimuli produced *increased* P200 amplitude, compared to non-target stimuli. This increase in P200 amplitude to targets in the FESz group is intriguing as this is generally thought to be precluded by the effects of the overlapping N200 component elicited by target stimuli. While the ADHD group showed increased P200 amplitude to T+1 compared with T-1 stimuli, the FESz group did not differentiate between non-target stimuli. The FESz group showed the same pattern of differentiation for P200 latency elicited to target vs. non-target stimuli, (earlier to target) as the normal control and ADHD groups. In addition, the comparison between non-target stimuli produced opposing results between the first episode and control groups with P200 latency elicited by T+1 stimuli prolonged compared with T-1 stimuli in the control group, but earlier in the first episode group.

P300 amplitude was reduced in FESz, compared to normal controls, in Study 2 (Chapter 5), however, in the current Study, the FESz group did not demonstrate a significantly reduced P300 amplitude when compared to the combined (clinical + normal) control group. This is because, across topography, the ADHD group

demonstrated reduced P300 amplitude compared with normal controls, a finding consistent with previous studies (Frank et al., 1998; Holcombe et al., 1986; Johnstone & Barry, 1996; Jonkman et al., 1997; Loiselle et al 1980; Overtom et al., Robaey et al., 1992; Satterfield et al., 1990). These findings have a number of important implications. Firstly, they reinforce doubts about the utility of P300 amplitude as a marker for schizophrenia because of its problems with specificity. Secondly, it may have theoretical implications for the reduction in P300 amplitude found in schizophrenia. For example, it may be associated with a generic impairment common to many psychopathologies, such as a working memory deficit. Alternatively, it may be sensitive to several different mechanisms in different psychiatric groups, each resulting in diminished P300. As might be expected from these findings, results from the discriminant function analysis demonstrated that patients with FESz were not accurately classified using N200 and P300 amplitude, when the control group included people with ADHD. As no left (compared with right) temporal deficit was found in the first episode group, it is unlikely that this would have increased the specificity of the P300 findings. The finding that P300 amplitude reduction is not specific to schizophrenia, challenges its usefulness as a biological marker for schizophrenia.

The discriminant analysis indicated that the P300 deficit is not specific for schizophrenia while deficits in N100, P200 components were specific for schizophrenia when compared with the combined group of controls and patients with ADHD. The most compelling evidence for this was that only the N100 and P200 variables were chosen in the stepwise DA which combined, the variables chosen in the individual stepwise

analyses for (i) N100 and P200 and (ii) N200 and P300. This finding highlights the possibility that N100 and P200 components to target and non-target stimuli may provide a more useful biological marker for genetic research than the traditional focus on P300 amplitude.

An obvious limitation of this Study was the lack of female participants. This was a consequence of the all-male ADHD group, as ADHD is much more common in males than females. It would be important to replicate these findings in a larger study, with equal female and male participants included.

This Study has demonstrated the benefits of using non-target, in addition to target ERPs, and in further separating ERPs elicited by non-target stimuli into those occurring immediately before the target stimulus (T-1), and those occurring immediately after the target stimulus. It was the distinct pattern of ERP responses to N100 and P200 elicited by T-1, target and T+1 stimuli found in the FESz group compared to the control and ADHD groups, that allowed the accurate discrimination of patients with FESz from a combination of normal and psychiatric, (ADHD) control groups.

## 8 THESIS CONCLUSIONS AND IMPLICATIONS

### 8.1 MAJOR FINDINGS AND IMPLICATIONS

This thesis has emphatically demonstrated the importance of looking beyond the P300 component in schizophrenia research. This is in contrast to earlier ERP research which focussed on the P300, because of its assumed association with critical cognitive variables and the robustness of the P300 amplitude reduction finding in schizophrenia.

The first major finding was that the early ERP components elicited by both non-target and target stimuli were disturbed in schizophrenia. ERPs to non-target stimuli showed reduced N100 amplitude and delayed P200 latency, while ERPs to target stimuli showed reduced and earlier N100 and increased P200 amplitude. A related finding, also revolving around the N100 and P200 components was the lack of differentiation between early ERP responses elicited by target and non-target stimuli in schizophrenia. Study 1 demonstrated that both of these deficits were reliably found in a large sample of patients with schizophrenia and their matched controls. In Study 2, these initial findings were extended with results indicating that the pattern of deficits also occurred among first episode schizophrenia participants.

The presence of these early deficits in both FESz and chronic schizophrenia suggests that they are more likely to be trait deficits, rather than transient state markers associated with severity of psychopathology, or other effects of illness or institutionalisation. Although reduced N100 amplitude to non-target stimuli in

schizophrenia has been found in some previous studies, the current series of studies that has tested large numbers of patients, in early and later stages of schizophrenia, and has used normal and clinical control groups, constitutes the most most comprehensive and compelling data-set about early ERP deficits in schizophrenia known to be reported.

These findings have important empirical implications for schizophrenia research. They indicate the importance of systematic analysis of N100 and P200 ERPs elicited by non-target stimuli. Secondly, they show that an examination of the relationship between these components elicited by non-target and target stimuli yields valuable information, and, therefore, should be included in the analysis.

A third major finding was that differences in the ERP response to non-target stimuli which occur before and after the target stimuli (T-1 & T+1) evident in the normal controls, was notably absent in both the first episode and chronic schizophrenia groups. The N100 reduction to T+1 compared with T-1 stimuli found fronto-centrally in normal controls was not present in chronic schizophrenia and was minimal in FESz (Study 2, Chapter 5). The N100 amplitude reduction associated with T+1 and observed in normal controls is consistent with findings of other oddball studies in the literature (Hirata & Lehman, 1989; Starr, Sandroni, & Michalewski, 1995; Starr et al., 1997) in which the target stimuli is always followed by a non-target stimuli by design or by virtue of low probability. The reason for this finding among normal controls has remained unclear, with the results being consistent with either response recovery or stimulus predictability hypotheses. However, Study 3 demonstrated that the effect disappeared when the non-

target status of the stimulus was not predictable, thereby ruling out the recovery hypothesis. Thus these studies confirm the T+1 effect on N100 amplitude in normals and more convincingly link it to the predictable occurrence of a task-irrelevant (non-target) stimulus.

The reduced N100 amplitude to T+1 stimuli finding has important empirical implications for ERP research for schizophrenia and as well as in normal and other clinical groups. From an empirical perspective, it demonstrates that it is important not to average ERPs to all non-target stimuli in the auditory oddball paradigm as certain non-target stimuli may have different functional significance. Among other possible interpretations, these findings could be seen to support a deficit in associative learning in schizophrenia and can be seen as support for the cognitive model proposed by Gray, Hemsley and others (Gray et al., 1991; Gray, 1998; Hemsley, 1996), that people with schizophrenia fail to establish appropriate response biases because they are unable to use stored memories of regularities based on their previous experience. An alternative possibility is that patients with schizophrenia, like normal controls, are aware that T+1 are non-target occurrences, but are unable to prevent these irrelevant stimuli from automatically capturing valuable attentional resources.

A fourth, and perhaps the most important finding of this thesis, is the improved sensitivity and specificity of deficits in the N100 and P200 components elicited by target and non-target stimuli when compared to the N200 and P300 measures. These results were both robust and reliable and the superior classification associated with the earlier

components between schizophrenia and normal control subjects in Study 2 were replicated in Study 4 between FESz and both clinical (ADHD) and normal controls.

In Study 4, N100 and P200 components elicited to target and non-target stimuli, utilising a stepwise DfA, enabled correct identification of 85% of the FESz subjects, and 82.5% of the combined (clinical + normal) controls. On the other hand, the use of N200 and P300 components to target stimuli in a stepwise DfA resulted in correctly classifying 65% of the FESz group and 55% of the combined (clinical+normal) control group. These classification rates appear impressive. If replicated, they have important empirical implications for genetic studies searching for a psychophysiological endophenotype. Currently reduced P300 amplitude has been considered as a likely endophenotype or biological marker for genetic studies with schizophrenia. However the results of Study 4 (Chapter 7) indicate that the N100, P200 components may be a superior biological marker than P300.

This thesis also examined the relationship between symptom factors and ERP components elicited by target and non-target stimuli. The most robust relationship was the negative correlation between the magnitude of N100 amplitude and the disorganisation factor, which is seen as a core feature of schizophrenia. This correlation was maximal for N100 amplitude to non-target stimuli. This suggests the possibility that the N100 amplitude to non-target stimuli may be related to the unique pathology of schizophrenia. In contrast, no significant correlations were found between symptom factors and P300 amplitude in this Study, and the results of previous investigations have been mixed and difficult to replicate.

The finding that people experiencing their first episode of schizophrenia have psychophysiological disturbances of a similar severity to those who have experienced schizophrenia over a number of years also has treatment and theoretical implications. With regard to treatment this finding emphasizes the need for an early and comprehensive intervention in schizophrenia. One further advantage of having the chronic schizophrenia group in addition to the FESz group was that it allowed for an exploration of differential age effects on ERPs to target and non-target stimuli between the two groups. The schizophrenia group did not show an exacerbation of the normal age effects on ERP components, providing an additional argument against the notion that schizophrenia is a neurodegenerative disorder.

Finally, preliminary evidence suggested that the P300 amplitude was sensitive to alternating sequences of stimuli within the oddball task, and systematically increased or decreased depending on whether these alternations discontinued or continued. Study 3 examined the proposal that, in these circumstances, reliable P300 changes to DA series would be a reliable index of associative strength in normal controls and would be impaired in schizophrenia. The results failed to confirm that such a pattern occurred in normals, hence the hypothesis could not be confirmed in schizophrenia. In any case, the study examined *DR* and DA effects in a comprehensive way in first episode schizophrenia, thereby contributing to the very limited research in this area. The finding that manipulations of the *DR* series has comparable effects on both normal controls and schizophrenia groups, suggests that the temporal determinants (such as target-to-target



intervals) that underpin these amplitude changes in normals, are not critical to the impairment in schizophrenia.

## 8.2 LIMITATIONS AND FUTURE DIRECTIONS

There are a number of study limitations. The participants with FESz, had commenced medication at the time of testing, so that while they had not had an extended time on medication and while medication was a covariate in the statistical analysis, it would be preferable to have tested these participants drug naïve and to have withdrawn the chronic schizophrenia participants from medication. This is difficult to achieve because of the serious ramifications of withholding medication for people with schizophrenia. However one possible way to overcome this would be to have a laboratory on the psychiatric admission ward, with the EEG recording a standard part of the initial neuropsychiatric battery prior to medication. At any rate, previous research has indicated that ERP component deficits are not due to the effects of medication (see Chapter 2.4.1) and as all significant results remained unchanged even after co-varying for medication, it appears very unlikely that the results were due to medication effects.

The thesis necessarily employed a cross-sectional rather than longitudinal design. Future investigation, following subjects from their first episode of schizophrenia in a longitudinal study, would provide important information on ERP deficits over the course of the illness.

Study 4 demonstrated the specificity of target and non-target N100, P200 deficits in first episode and chronic schizophrenia. However in addition to the need for replication of these findings, it would also be important to demonstrate that these deficits were present in people prior to the onset of their schizophrenia illness and more prevalent in family members, to be able to consider these deficits as biological markers.

The ADHD group provided an appropriate clinical control group to examine initially the specificity of schizophrenia deficits as both groups have cognitive and P300 reduction deficits in common. Future investigations might extend this research by including additional psychiatric control groups to provide a more detailed examination of the specificity of the findings. A further limitation to Study 4, was the lack of female participants, due to the constraints of an all male ADHD group, thus limiting generalisation of findings to a male population. Further investigation, with adequate numbers of female participants, is required.

The ERP topographical analysis in Study 2 although providing a high temporal resolution of brain activity, is limited in its spatial resolution. The neural basis of deficits in schizophrenia could be further explored using neuroimaging techniques, such as event related (er) fMRI, allowing for much greater spatial resolution of cortical and sub-cortical areas. For example, an erfMRI study by Kiehl and Liddle (2001) has been able to demonstrate reduced activations, both in strength and extent, in right lateral frontal cortex, thalamus, bilateral anterior superior temporal gyrus, anterior and posterior

cingulate, associated with target processing in schizophrenia compared to normal controls.

Study 4 clarified answers to competing hypotheses arising from the N100 amplitude reduction to T+1 stimuli found in Study 2. However, probability differences in paradigms existed between the two studies - 0.5 in Study 3 and 0.3 in Study 2, which may have affected results. This difference arose, in part, from the constraints imposed by having the target stimuli followed equiprobably by target and non-target stimuli, and by the sequence requirements of Study 3. However a previous study (Polich & Bondurant, 1997) did not find N100 amplitude non-target sequence effects in normal participants, when examining these effects in paradigms with 0.33 and the other with 0.67 target probabilities. This suggests that the probability difference between the two studies is unlikely to have affected findings.

### 8.3 CONCLUSION

This thesis provides a thorough investigation of target and non-target N100 and P200 components, in contrast to target N200 and P300 components, from the first onset of schizophrenia, through chronic duration, and in comparison with both healthy controls and ADHD. The results present compelling evidence that N100 and P200 components to target and non-target stimuli are impaired in both the early and chronic manifestations of schizophrenia and demonstrate the importance of investigating non-target in addition to target ERPs in schizophrenia. In contrast to reduced P300 amplitude, deficits in these early components to both target and non-target stimuli show superior sensitivity and

specificity for schizophrenia, and hence may serve as potentially useful biological markers for the disorder.

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## 10 APPENDICES

## 10.1 APPENDIX 1- CHLORPROMAZINE EQUIVALENT

This table shows the dosage estimates used to calculate the Chlorpromazine equivalent medication levels in patients in this thesis (Lambert, 1998).

ORAL MEDICATIONS 100 CHLORPROMAZINE EQUIVALENTS	
Haloperidol	2
Trifluoperazine	5
Pimozide	1.5
Pericyazine	10
Fluphenazine	2
Thioridazine	100
Respiridone	1.5
Olanzapine	3
Clozapine	75
Thiothixene	4
Depot Injections (2 Weekly)	300 Chlorpromazine Equivalents per Day
Fluphenazine Decanoate	25
Haloperidol Decanoate	50
Zuclopenthixol Decanoate	200
Flupenthixol Decanoate	40

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# Target and non-target ERP disturbances in first episode vs. chronic schizophrenia

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## Abstract

**Objectives:** Event-related potential (ERP) abnormalities to target stimuli are reliably found in schizophrenia. However, as people with schizophrenia are thought to have difficulty discerning the relevance of incoming sensory stimuli it is also important to examine ERPs to non-targets. To differentiate between potential trait markers of the disease and deficits that might be associated with the consequence of illness chronicity, this study investigated ERPs to both target and non-target stimuli in groups of people with either first episode or chronic schizophrenia (CSz).

**Methods:** Using an auditory oddball paradigm, ERPs to target, non-target before target (Nt before) and non-target after target (Nt after) stimuli were analysed for 40 patients with CSz, 40 patients with first episode schizophrenia (FESz) and two groups of normal controls matched for age and sex with their patient counterparts.

**Results:** The FESz group showed the same pattern of amplitude disturbance as the CSz group to both targets (reduced N100, N200, P300 and increased P200) and non-targets (reduced N100) compared to controls. Both CSz and FESz groups also failed to show the changes to the P200—N200 component between targets and non-target stimuli that was exhibited by controls (smaller earlier P200 to targets vs. increased delayed P200 to non-targets) or the reduction in N100 amplitude of ERPs to the Nt after stimuli compared with ERPs to the Nt before stimuli. Previous literature has focussed on the sensitivity of P300 deficits in classifying persons into schizophrenia and non-schizophrenia groups. This study demonstrated improved accuracy in the classification of patients with schizophrenia from controls using discriminant analysis of target and non-target N100 and P200 components.

**Conclusions:** The results suggest that ERP disturbances are evident at the time of first referral to mental health services and may be a potential trait (rather than secondary effect) of the illness. It is important to include both target and non-target stimuli processing, and their interrelationship in future research. Crown Copyright © 2002 Published by Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** Schizophrenia; First episode schizophrenia; Event-related potential; Non-target

## 1. Introduction

Numerous studies have found deficits in event-related potentials (ERPs) of patients with schizophrenia, linked to target stimuli in an auditory oddball paradigm, most notably a reduction in P300 amplitudes (for reviews see Pfefferbaum et al., 1989; Pritchard, 1986; Ford et al., 1992; Jeon and Polich, 2000). Most of these studies have investigated ERPs in chronic patients, however, an important emerging issue is whether these deficits are trait-like and therefore present at the onset of illness (Salisbury et al., 1998; Ford,

1999; Frodl-Bauch et al., 1999; Mathalon et al., 2000; Blackwood, 2000). This is particularly important because ERP deficits observed in patients with chronic schizophrenia (CSz) may be secondary effects of chronic morbidity, neuroleptic medication or other changes associated with chronic mental illness (e.g. hospitalisation). If established as a trait, ERP deficits could be useful in identifying 'at risk' individuals and would provide potential for the implementation of preventative strategies.

Although there is now some evidence that reduced P300 amplitude is a stable trait marker in schizophrenia (Mathalon et al., 2000; Blackwood, 2000), with evidence for genetic association (Blackwood et al., 2001; Weisbrod et al., 1999), there have been studies which have not found

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reduced P300 in the undiagnosed family members of people diagnosed with schizophrenia (Friedman et al., 1988) and in a study that looked at the predictive validity of the P300, Squires-Wheeler et al. (1993) did not find P300 amplitude reduction predictive of subsequent schizophrenic breakdowns. However, in the Squires-Wheeler et al. study (1993), as might be expected, because of the relatively low incidence of schizophrenia even among relatives of schizophrenics, there were no more than 6 subjects classified as having a schizophrenic breakdown and only one classified with schizophrenia disorder (this subject's P300 amplitude was reduced one and a half standard deviations below the mean for the normal group). Hence, the reliability of these findings is questionable, and the importance of using alternative methods to determine whether ERP deficits observed among chronic schizophrenics is trait-like is further highlighted. One such method comprises the comparison of ERP deficits early (first presentation) and late (CSL) in the developmental course of schizophrenia. Reduced mismatch negativity (MMN) amplitude has also been found in non-psychotic first degree relatives of patients with schizophrenia (lessen et al., 2001) suggesting that earlier components (N100 and P200) should also be investigated. There have been few studies investigating auditory oddball ERP deficits in people with first episode schizophrenia (FESz). Salisbury et al. (1998) and Hirayasu et al. (1998) have both found reduced P300 amplitude to target stimuli in this group. ERPs to non-target stimuli (and their relationship with target ERPs) remain unexplored in FESz.

There are both theoretical and empirical indications for investigating possible ERP disturbances to non-target stimuli in addition to target stimuli in people with schizophrenia. Current models of information processing deficits in schizophrenia (e.g. Frith, 1995; Gray, 1998; Hemsley, 1996) suggest a disturbance at the 'comparator' level in the match/mismatch between incoming stimuli and stored memories of past regularities or similarly, a failure in the inhibitory effect of context (Servan-Schreiber et al., 1996). These models highlight the need to examine the processing of irrelevant or context information in addition to relevant information in people with schizophrenia. Houghton and Tipper's (1996) model of 'normal' selective attention proposes that, in addition to the excitatory feed back loop elicited by target stimuli, selective attention involves an inhibitory feedback loop elicited by non-target stimuli. There is evidence from negative priming tasks indicating a disturbance of this inhibitory process in schizophrenia (Beech et al., 1989, 1991). In the auditory oddball paradigm, where subjects are asked to respond to target and not to non-target stimuli, ERPs to non-targets may provide insight into this inhibitory process, and should be investigated along with ERPs to targets. As the auditory oddball paradigm comprises target events that often follow a series of non-target occurrences, a comparison of ERPs elicited by targets and those elicited by non-targets immediately preceding and following the target stimuli might capture the effects of

cognitive processes during the putative comparator stage (P200—N200) and immediately before (N100) and after (P300) such processing.

Further evidence of the significance of non-target stimuli for information processing emerges from studies, showing that the same stimuli are processed differently when they appear as a non-target in the auditory oddball task than when they are used in a passive listening condition (Garcia-Larrea et al., 1992; Yordanova et al., 2001). There is also evidence that ERPs to non-targets before (Nt before) and after (Nt after) the target stimuli, in normals, may involve different brain states (as indicated by different scalp topographical distributions for the two types of non-targets) and should be averaged separately (Hirata and Lehmann, 1990). ERPs to Nt after stimuli may also provide insight into the possibility of a disturbance in temporal recovery (Roth and Cannon, 1972) or refractoriness in N100 (Shelley et al., 1999), which has been suggested in schizophrenia. Additionally, there is the possibility of an expectancy effect associated with the Nt after stimuli, as a target stimulus is always followed by a non-target stimulus in the oddball design used in this study. For these reasons, in our study, we have examined separately Nt before and Nt after the target stimuli.

Reported findings in non-target ERPs in people with schizophrenia include reduced N100 amplitude (Roth et al., 1980; Pfefferbaum et al., 1989; Ogura et al., 1991; Boutros et al., 1997; Laurent et al., 1999; Brown et al., 2000); both increased (Pfefferbaum et al., 1989; Ogura et al., 1991) and reduced (Roth and Cannon, 1972; Roth et al., 1980; McCarley et al., 1991) P200 amplitude; earlier P200 latency (Brown et al., 2000) and less difference between target and non-target N100/P200 components (Brown et al., 2000). Studies by Brown et al. (2000) and Roth and Cannon (1972) indicate the importance of examining the group by stimuli interaction, as patterns of differences between ERPs to target and non-target stimuli found in normal controls may not be present in schizophrenia. There is also complementary evidence of a disturbance of target/non-target discrimination from single trial ERP analysis showing people with schizophrenia had fewer P300s to targets and more P300s to non-targets compared with controls (Roschke et al., 1996; Wagner et al., 2000).

Previous literature has focussed on the sensitivity of the P300 component in schizophrenia. For example, Ford et al. (1992) established criterion P300 amplitude, above which one can rule out a diagnosis of schizophrenia. Boutros et al. (1997), however, found that non-target N100 and P200 components were also sensitive measures and recently Ford et al. (2001) proposed that N100 amplitude reduction to targets and non-targets may have greater specificity for schizophrenia than P300 reduction (in that study while P300 amplitude was sensitive to schizophrenia-like symptoms found both in schizophrenic and in epileptic patients, with interictal CSz-like features, only N100 was specific to those symptoms in schizophrenia alone). We investigated the

sensitivity of the N100 and P200 components elicited by non-targets and targets and compared this with the P300 component to targets in discriminating CSz and FESz groups from their respective normal control groups. Following Gray's (1998) model and our (Brown et al., 2000) previous finding that there is less difference between target and non-target N100 and P200 scores in a schizophrenia, we decided to also investigate the sensitivity of the within group differences for stimuli (where these differed between the groups) by subtracting target and non-target scores.

## 2. Methods

### 2.1. Participants

#### 2.1.1. Participants with chronic schizophrenia

Forty people (28 males, 12 females) with CSL, aged between 23 and 51 years of age, with a mean age of 36.0 years (SD = 7.1 years) were recruited from hospital and community health centres. All participants had been diagnosed with schizophrenia for at least 4 years (range 4–34 years) with a mean duration of illness of 14.3 years (SD = 7.0 years). All were medicated, with 20 subjects on typical antipsychotics (mostly depot preparations), 7 on atypical antipsychotics and 13 on clozapine. The mean dose of medication was 520 chlorpromazine equivalents (SD = 423). Diagnosis was made by concordance between the case file diagnosis and diagnosis based on Section G (schizophrenia and psychotic disorders) of the Composite International Diagnostic Interview (World Health Organisation, 1992), or by concordance between diagnosis made by two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders (3rd edition revised) (DSM-III-R) (American Psychiatric Association, 1987). Exclusion criteria were a recent history of substance abuse, past history of substance dependence, mental retardation, other neurological disorders including epilepsy and head injury (defined as an injury requiring hospital observation for at least 4 h or unconsciousness for more than 1 h).

#### 2.1.2. Participants with first episode schizophrenia

Forty people (26 males, 14 females) with FESz aged between 14 and 26 years (mean = 19.6 years; SD = 3.2 years), were recruited from community and hospital settings through the Western Sydney First Episode Psychosis Project. FESz participants were defined as those young people presenting for the first time to health services with psychotic symptoms that warranted a diagnosis of either schizophrenia or schizophreniform disorder. Diagnosis was made by means of a consensus conference (of at least 3 fully qualified psychiatrists) that drew upon the interview by the participating psychiatrist, information from family and case manager and the case notes. Diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM-IV) (Amer-

ican Psychiatric Association, 1994). Exclusions were the same as for the chronic group. The majority of participants were medicated with atypical antipsychotics alone ( $M = 250$  chlorpromazine equivalents; SD = 202), though a small number were also receiving antidepressant or anticholinergic medications. Four participants were on no medication.

#### 2.1.3. Positive and negative symptom scale (PANSS)

Schizophrenic symptoms were rated for both CSz and FESz groups using the Positive and Negative Syndrome Scale (PANSS, Kay and Opler, 1987). The CSz group had a mean total score of 78.5 (SD = 18.7) and the FESz group 75.2 (SD = 15.1). Mean (SD) subscale scores for the CSz group were: positive, 20.3 (SD = 6.5); negative, 20.6 (SD = 6.5); and general, 37.6 (SD = 8.3); and for the FESz group: positive, 17.2 (SD = 5.7); negative, 19.5 (SD = 6.2); and general, 38.7 (SD = 6.9).

#### 2.1.4. Normal control participants

Normal control participants for the two groups were recruited from the community and were gender and age matched to within 2 years for clinical subjects under the age of 25 years and to within 5 years for those over the age of 25 years. The rationale for closer age matching of the younger subjects derived from research indicating maturational changes in the electroencephalogram (EEG), occurred up to early adulthood (Neidermeyer, 1999). Control group 1 with a mean age of 36.7 years (SD = 7.6) was compared with the CSz group and control group 2 with a mean age of 19.65 years (SD = 3.86) was compared with the FESz group. Persons with a recent history of substance abuse, or past history of substance dependence, epilepsy, other neurological disorders, mental retardation or head injury were excluded from the sample.

## 2.2. Data acquisition

Participants were seated in a reclining chair in a quiet, dimly lit laboratory, facing a video screen and wearing a pair of headphones. A conventional auditory oddball paradigm was employed, consisting of 40 target tones (1500 Hz with 15% probability and 247 background (1000 Hz) tones both lasting 50 ms (with 10 ms rise and fall). The tone intensity was 60 dB SPL and the fixed interstimulus interval (ISI) was 1.3 s. Participants were asked to look at a dot on the computer screen 60 cm in front of them, ignore the low (background) non-target tones and press two reaction time buttons (with the index finger of each hand, to counterbalance motor activity) when they identified a task relevant target tone. Task instructions emphasised speed and accuracy of response equally. EEGs were recorded on a DC based system (Synamps, equipped with a 16 bit A/D converter) from 19 scalp sites according to the 10–20 International system (Bloom, 1982) in reference to linked-ear electrodes with an amplification of 200, a band pass from 0 to 50 Hz

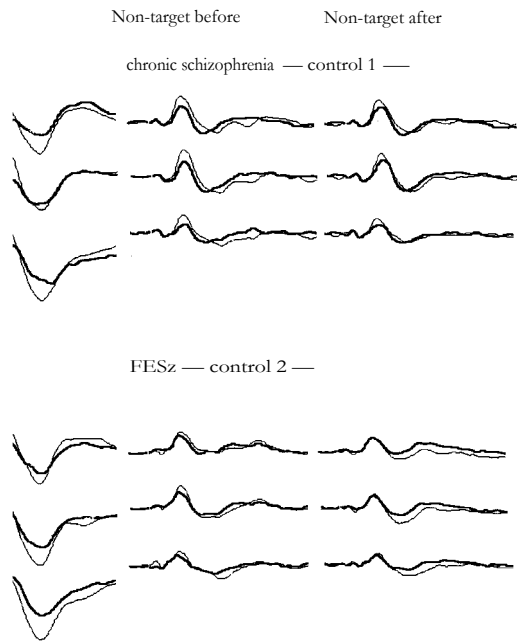


Fig. 1. Grand average waveforms for all groups, to each stimuli at midline sites. Both chronic and first episode Sz groups show reduced N100, N200 and P300 and increased P200 amplitude to targets compared with controls and decreased N100 amplitude with Nt before. Chronics showed delayed P200 latency to targets and earlier P200 latency to non-targets and delayed N200 latency to targets.

and digitised at 250 Hz. Only data recorded at Fz, Cz and Pz are reported here. Horizontal electro-oculogram (EOG) was recorded via electrodes placed at the outer canthus of each eye and vertical EOG was recorded via two electrodes placed 1 cm above and below the midline supraorbital and infraorbital regions of the left eye. Eye correction was carried out using a technique based on Gratton et al. (1983). Within the block comprising target and non-target tones, in 33 instances, targets occurred both immediately before and after the target tone and the responses to these 33 targets, 33 non-targets before (Nt before), and 33 non-targets after (Nt after) were averaged separately (in 7 instances the non-targets were immediately preceded by and followed by a target and hence were simultaneously both Nt before and Nt after, and so were excluded). For targets N100, P200, N200 and P300 peaks were measured relative to a prestimulus (200 ms) baseline by an automated system based on the detection of a consistent change in the direction of the gradient of the waveform (Haig et al., 1995). Thus a change from a consistently positive to a consistently negative gradient was identified as a positive peak, and vice versa for a negative peak (Haig et al., 1995). In addition, the criteria that N100 occurred between 80 and 140 ms, P200 between 150 and 240 ms, N200 between 200 and 280 ms and P300 between 250 and 500 ms. Peaks thus identified were then verified through visual inspection. N100 and P200 peaks in averaged ERPs to non-targets before and after were ascertained according to the same method.

## 2.3. Analysis

### 2.3.1. Midline ERPs

N100 and P200 amplitudes and latencies were submitted separately to a 3-way analysis of variance (ANOVA) repeated measures design, incorporating two groups (schizophrenic vs. controls) X 3 electrode sites (Fz, Cz, Pz) X 3 stimuli (Nt before, target and Nt after) with repeated measures for electrode and stimulus factors. When sphericity assumptions were violated, the Greenhouse–Geisser correction was employed and the degrees of freedom (df) values were appropriately adjusted. N200 and P300 components were reliably observed only to the target stimulus and were therefore subjected to a group (schizophrenia vs. controls) X site (Fz, Cz, Pz) ANOVA repeated measures design. These analyses were done separately for the CSz group vs. control 1 group and FESz group vs. control 2 group. The Statistical Package for Social Sciences 9.0 program (SPSS Inc., 1999) was used in all analyses. Significant main and interaction effects based on multiple df were further analysed by post-hoc comparisons with Bonferroni adjusted alpha level. ERP components were also submitted to a 3-way ANOVA repeated measures for chronic vs. FESz groups and for control 1 vs. control 2 group. Medication and age (used when comparing FESz and CSz groups, because between groups, ages differed markedly in this analysis) were used as covariates.

### 2.3.2. Discriminant function analysis (dfa)

Dfa was performed in two stages. Stage 1 related to amplitudes and latencies of components derived conventionally, and stage 2 related to N100 and P200 difference score amplitudes and latencies. Component amplitude and latency measures on which the clinical and control groups were significantly different were entered into a stepwise dfa for the CSz and FESz groups and their controls separately in the following manner.

#### 2.3.2.1. Stage 1.

1. N100 and P200 component amplitudes and latencies for target, Nt before and Nt after. Where the number of significant differences exceeded the number of variables permissible under subject-to-variable ratio recommendations, and differences were observed at more than one site, then only the site at which the component has maximal amplitude/latency was entered (e.g. Cz for P200).
2. All target P300 amplitudes and latencies at midline sites.
3. Variables arrived at by the stepwise procedure above combined with significant N200 differences. Fisher classification functions from the CSz dfa were then applied to the FESz group to test the robustness of the dfa replicated in an independent sample.

2.3.2.2. Stage 2. Consistent with some current theories, critical dysfunctions in schizophrenia could relate to mechanisms that are called into play when switches from

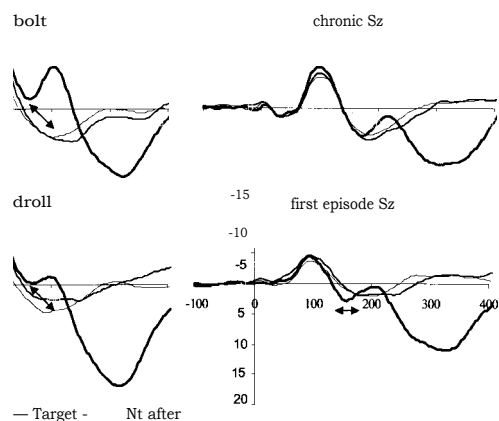


Fig. 2. Superimposed grand average waveforms for ERPs to target, Nt before and Nt after stimuli for each group at Cz. Arrows on control graphs refer to N100 amplitude reduction and P200 amplitude and latency shift between targets and non-targets. These patterns are not found in the CSz group and only the P200 latency shift is found in the FESz group.

one stimulus to another occur, such as when a target follows a non-target or vice versa. Such processes may be best captured by difference scores rather than by ERP peaks derived independently for target and non-target stimuli. Difference scores were computed and these values were entered into a dfa to determine whether these measures would be as sensitive as conventionally derived measures to predict group membership.

### 2.3.3. Reaction time

Reaction times for CSz vs. control, FESz vs. control, CSz vs. FESz, and control 1 vs. control 2 were compared by *t* test.

## 3. Results

ERP waveforms are presented in Fig. 1 (between group) and Fig. 2 (within group) and amplitude and latency values in Table 1. A small percentage (between 1 and 2.5% in each group) of ERP measures were identified as outliers (greater or less than one and a half the interquartile range from the upper and lower quartile). All results subsequently are based on data with outliers; however, results remained significant following removal of outliers and covarying for medication (chlorpromazine equivalents).

### 3.1. ERPs

#### 3.1.1. N100

**3.1.1.1. CSz vs. controls.** There were significant main effects for group,  $F(1,78) = 25.33$ ,  $P < 0.001$ , the CSz group showing reduced N100 amplitudes overall; stimulus  $F(2, 77) = 10.69$ ,  $P < 0.001$ , larger N100 amplitude to target than non-target stimuli and site,  $F(1.63, 126.94) = 130.34$ ,  $P < 0.001$ , with N100 amplitude maximal fronto-centrally. There was also a significant group X stimulus X site interaction,  $F(2.83, 220.97) = 2.89$ ,  $P < 0.05$ . The interaction arose

because N100 amplitudes were significantly larger for target stimuli than for Nt after stimuli, for the control, but not the CSz group (site interactions can be seen in Tables 1 and 2). There was a significant stimuli X group interaction,  $F(2, 77) = 4.38$ ,  $P < 0.05$ , for N100 latency which arose because N100 amplitude for Nt after stimuli was significantly earlier than for target or Nt before stimuli in the control, but not the CSz group, and a main effect for site,  $F(1.63)130.34$ ,  $P < 0.001$  with earliest latency at Pz.

**3.1.1.2. FESz vs. control.** There were significant main effects for group,  $F(1,78) = 9.57$ ,  $P < 0.01$ , the FESz group showing reduced N100 amplitudes overall; stimulus,  $F(1.82,142.34) = 15.83$ ,  $P < 0.001$ , larger N100 amplitude to target than non-target stimuli and site,  $F(1.39,108.73) = 76.42$ ;  $P < 0.001$ , with N100 amplitude maximal fronto-centrally. There was also a significant group X stimulus X site interaction  $F(2.75, \ 215.09) = 15.376$ ,  $P < 0.001$ . The interaction arose because there were N100 amplitude changes as a function of stimuli (target > Nt before > Nt after) in fronto-central sites for the control, but not the FESz group.

#### 3.1.2. P200

**3.1.2.1. CSz vs. control.** There was a significant group X stimulus X site interaction  $F(3.32, 258.73) = 7.86$ ,  $P < 0.001$  for P200 amplitude. The CSz group had significantly larger P200 amplitude for target stimuli than controls which explains the main effect for group,  $F(1,78) = 12.21$ ,  $P = 0.001$ . The interaction arose because there was a stimulus effect, significantly reduced P200 amplitude to target than to non-target stimuli, found in controls but not in the chronic group which explains the main effect for stimulus  $F(2,77) = 11.21$ ,  $P < 0.001$ . Site interactions can be seen in Table 1. There was a significant stimulus X group interaction  $F(2, 77) = 119.75$ ,  $P < 0.001$  for P200 latency. The CSz group was delayed for target, but earlier for non-target stimuli when compared with controls.

**3.1.2.2. FESz vs. control.** There was a group X stimulus interaction  $F(1.82,140.12) = 8.57$ ,  $P < 0.001$  and group X site interaction  $F(1.69, 129.97) = 3.86$ ,  $P < 0.001$  for P200 amplitude. The FESz group had larger P200 amplitude than controls for target stimuli and smaller P200 amplitude than controls for Nt after stimuli. The stimulus interaction arose from a stimuli effect found in controls but not in FESz, where P200 amplitude to target stimuli was smaller than P200 amplitude to non-target stimuli. Site effects can be seen in Table 1.

#### 3.1.3. N200/P300

**3.1.3.1. CSz vs. control.** There were significant main effects for group for N200 amplitude,  $F(1, 78) = 16.35$ ,  $P < 0.001$ , and latency,  $F(1, 78) = 31.88$ ,  $P < 0.001$ , with amplitudes

Table 1

N100 and P200 means (SDs) for CSz and controls (a), FESz and controls (b) and N200 and P300 values for all groups (Oa)

		Target		Non-target before		Non-target after	
		Control 1	CSz	Control 1	CSz	Control 1	CSz
<i>(a) N100 and P200 means for CSz and controls</i>							
N100 amp	Fz	-10.2(3.0)	-7.5(3.7)*	-9.1(2.6)	-5.6(4.2)*	-8.1(4.1)	-6.2(4.5)
	Cz	-11.4(3.8)	-7.1(3.6)*	-10.2(3.4)	-5.9(3.5)*	-7.5(3.6)	-5.9(3.2) <sup>1</sup>
	Pz	-6.6(3.1)	4.2(2.4)*	-6.2(2.7)	-3.5(2.1)*	-5.39(2.4)	-4.3(2.5)
N100 Lat	Fz	108.3(16.6)	106.6(14.9)	105.2(16.1)	104.9(12.6)	100.5(12.7)	105.7(16.8)
	Cz	103.1(13.2)	101.1(11.0)	103.0(11.4)	104.5(11.2)	95.5(9.7)	104.0(15.6)*
	Pz	101.0(12.6)	98.7(12.9)	101.8(12.1)	100.7(16.5)	98.6(13.0)	101.0(19.2)
P200 amp	Fz	0.8(3.7)	3.5(4.6)*	3.2(3.1)	4.7(4.1)*	3.4(4.3)	3.9(3.6)
	Cz	-0.4(4.7)	5.6(4.2)*	5.8(2.9)	6.1(3.2)	5.2(3.5)	5.2(3.4)
	Pz	1.5(3.3)	5.4(3.1)*	3.9(2.2)	5.4(2.9)	3.7(3.2)	3.5(2.7)
P200 lat	Fz	172.4(16.1)	178.5(15.3)	201.9(27.7)	185.9(21.4)*	199.7(26.4)	182.3(20.6)*
	Cz	161.7(18.6)	174.9(16.7)*	203.7(26.4)	182.6(19.0)*	200.5(23.4)	184.6(20.0)*
	Pz	163.2(17.4)	178.5(21.3)*	192.1(28.9)	187.1(27.5)	199.5(26.0)	181.1(21.9)*
<i>(b) N100 and P200 means for FESz and controls</i>							
		Control 2	FESz	Control 2	FESz	Control 2	FESz
N100 amp	Fz	-10.6(4.1)	-5.9(3.6)*	-7.5(4.0)	-6.3(2.8)	-5.5(3.5)	-5.6(3.5)
	Cz	-9.3(4.5)	-5.4(3.4)*	-7.7(3.9)	-5.5(2.8)*	-5.4(3.8)	-4.4(2.9)
	Pz	-4.8(2.7)	-3.9(3.1)	-5.2(2.7)	-4.0(2.5)*	-4.4(3.6)	-3.5(3.1)
N100 lat	Fz	110.4(16.7)	106.5(15.8)	110.7(20.3)	105.6(19.1)	106.9(17.5)	113.5(31.7)
	Cz	104.5(12.2)	97.1(15.0)	106.1(16.6)	101.5(18.1)	101.9(19.3)	102.6(17.4)
	Pz	96.2(9.6.2)	94.3(19.4)	101.2(19.0)	98.8(18.8)	100.1(16.4)	95.2(18.0)
P200 amp	Fz	-1.7(5.2)	2.3(4.7)*	1.5(3.9)	1.6(3.2)	3.3(3.9)	1.8(4.1)
	Cz	1.7(6.2)	4.0(4.5)	4.6(4.6)	3.8(3.4)	5.8(4.4)	3.0(3.9)*
	Pz	3.5(5.8)	4.5(3.8)	3.5(3.6)	3.2(3.0)	4.1(3.4)	2.2(3.0) <sup>1</sup>
P200 lat	Fz	171.9(17.3)	168.4(13.9)	186.2(37.2)	188.7(29.9)	185.4(20.3)	181.6(25.5)
	Cz	171.2(20.4)	165.8(16.6)	184.2(31.2)	192.8(28.0)	184.6(22.2)	179.1(26.7)
	Pz	160.8(31.7)	158.1(25.2)	185.8(34.6)	194.7(33.0)	184.6(23.2)	172.2(31.7)
<i>(c) N200 and P300 values for all groups</i>							
		Target					
		Control 1	CSz	Control 2	FESz		
N2 Amp	Fz	-5.3 ± 3.6	-3.9 ± 4.4	-9.9 ± 5.6	-5.8 ± 4.6*		
	Cz	-7.5 ± 5.9	-1.7 ± 4.8*	-3.2 ± 7.2	-0.9 ± 5.5		
	Pz	-2.1 ± 4.3	0.7 ± 3.4*	1.1 ± 5.3	0.8 ± 4.4		
N2 Lat	Fz	209.8 ± 16.6	229.5 ± 21.6*	214.1 ± 18.9	222.5 ± 19.8		
	Cz	207.2 ± 13.1	220.6 ± 18.2*	209.3 ± 18.1	216.1 ± 21.6		
	Pz	203.8 ± 22.3	226.5 ± 17.1*	195.1 ± 29.9	204.9 ± 31.0		
P3 Amp	Fz	10.3 ± 6.3	5.7 ± 5.9*	10.4 ± 8.5	7.9 ± 7.7		
	Cz	11.9 ± 8.0	11.2 ± 7.0	18.9 ± 10.6	13.3 ± 8.2*		
	Pz	18.9 ± 6.6	15.1 ± 6.6*	25.2 ± 10.5	17.7 ± 9.7*		
P3 lat	Fz	316.3 ± 23.4	315.5 ± 27.8	315.9 ± 28.8	320.4 ± 45.1		
	Cz	316.8 ± 23.7	309.2 ± 32.6	316.0 ± 35.8	317.7 ± 38.5		
	Pz	328.0 ± 21.6	327.4 ± 35.5	318.1 ± 27.6	325.4 ± 39.3		

<sup>a</sup> <sup>1</sup>P < 0.05, \*P < 0.01, Bonferroni adjusted alpha level.

for the CSz group being reduced and latencies being delayed. The reduction in N200 amplitude was prominent at both Cz and Pz but not at the Fz site as indicated by the group X site interactions,  $F(2, 77) = 10.15$ ,  $P < 0.001$ . The CSz group showed an overall reduced P300 amplitude demonstrated by a significant main effect for group,  $F(1, 78) = 5.87$ ,  $P < 0.05$ , with the reduction being prominent in both Fz and Pz sites but not at the Cz site as indicated by the site X group interaction effect,  $F(1.82, 141.83) = 5.19$ ,  $P < 0.01$ . There was also a main effect for site,  $F(1.82, 141.83) = 105.60$ ,  $P < 0.001$ , with P300 amplitude maximal at Pz.

**3.1.3.2. FESz vs. control.** There was a significant group X site interaction for N200,  $F(1.73) = 6.76$ ,  $P < 0.01$ , with the FESz group showing reduced N200 amplitude at Pc. The FESz group showed an overall reduced P300 amplitude demonstrated by a significant main effect for group,  $F(1.78) = 7.51$ ,  $P < 0.01$ , with the reduction being prominent at Cc and Pc sites as indicated by the group X site interaction  $F(1.53) = 6.05$ ,  $P < 0.01$ . There was also a main effect for site,  $F(1.53, 119.00) = 140.21$ ,  $P < 0.001$ , with P300 amplitude maximal at Pz.

Table 2

Significant within-group differences for target (T), non-target before (Nt-b) and non-target after (Nt-a) stimuli<sup>a</sup>

		Control 1	CSz	Control 2	FESz
N100 amp	Fz	T > Nt-a	T > Nt-b <sup>1</sup>	T > Nt-b > Nt-after	
	Cz	T > Nt-b > Nt-a		T > Nt-b > Nt-after	
	Pz	T > Nt-a <sup>†</sup>			
N100 lat	Fz	T > Nt-a <sup>†</sup>			
	Cz	T > Nt-a, Nt-b > Nt-a			
	Pz				
P200 amp	Fz	T < Nt-b, T < Nt-a		T < Nt-b and Nt-a, Nt-b < Nt-a	
	Cz	T < Nt-b, T < Nt-a		T < Nt-b <sup>1</sup> and Nt-a	
	Pz	T < Nt-b, T < Nt-a	T > Nt-a		T > Nt-a
P200 lat	Fz	T < Nt-b, T < Nt-a		T < Nt-a	T < Nt-b and Nt-b <sup>1</sup>
	Cz	T < Nt-b, T < Nt-a		T Nt-a <sup>1</sup>	T < Nt-a < Nt-b <sup>1</sup>
	Pz	T < Nt-b, T < Nt-a		T < Nt-b and Nt-a	T < Nt-b, Nt-a < Nt-b

<sup>a</sup>  $P < 0.01$  for all except for <sup>1</sup> indicates  $P < 0.05$ , Bonferroni adjusted alpha level.

**3.1.3.3. CSz vs. FESz.** For target P300 amplitude, significant differences found between the two control groups (which did not remain significant after effects of age were partialled out) were not found between the CSz and FESz groups. Thus, not only did the group with FESz show reduced P300 amplitude when compared with their controls, but also the age related differences in P300 amplitude that one might have expected to find when compared with the CSz group were not apparent.

### 3.2. Discriminant function analysis

#### 3.2.1. Stage 1

**3.2.1.1. N100, P200.** Stepwise discriminant analysis with significant between group target and non-target variables was able to accurately classify 85% of the CSz group and 77.5% of their control group, Wilk's  $A(3,78) = 0.51$ ,  $\chi^2 = 51.52$ ,  $P < 0.001$ , using only the following variables, with standardised canonical discriminant function coefficients in brackets: target P200 amplitude (0.50), Nt before N100 amplitude (0.63) and Nt before P200 latency (-0.54). For the FESz group this procedure accurately classified 77.5% of the clinical group and 75% of their controls, Wilk's  $A(1,78) = 0.722$ ,  $\chi^2 = 25.30$ ,  $P < 0.001$ , using only target N100 amplitude (1.00).

**3.2.1.2. P300.** Stepwise discriminant analysis with all midline P300 components was able to correctly identify 70% of the CSz group and 77.5% of their control group, Wilk's  $A(3,78) = 0.72$ ,  $\chi^2 = 25.32$ ,  $P < 0.001$ , using P300 amplitude at Pc (1.03), Cc (-1.35) and Fz (1.01). Similarly, 72.5% of the FESz group and 57.5% of their controls, Wilk's  $A(1,78) = 0.88$ ,  $\chi^2 = 10.235$ ,  $P = 0.001$ , were able to be correctly identified using P300 amplitude at Pc (1.00).

**3.2.1.3. All components.** Stepwise discriminant analysis using the variables from the analysis previously and adding significant between group N200 variables (again so

as not to exceed the subject to variable ratio these were limited to the maximal N200 site Fz) was able to accurately classify 90% of the CSz group and 75% of their controls, Wilk's  $A(4,78) = 0.48$ ,  $\chi^2 = 55.27$ ,  $P < 0.001$ , using Nt before N100 amplitude (0.51), Nt before P200 latency (-0.50), target P300 amplitude (-0.33) and target P200 amplitude (0.53). For the FESz group 77.5% of the clinical group and 72.5% of their controls, Wilk's  $A(2,78) = 0.67$ ,  $\chi^2 = 31.12$ ,  $P < 0.001$  using target N100 amplitude (0.85) and target P300 amplitude (-0.48). Discriminant analysis applying the Fisher classification functions of the CSz group stepwise analysis to the independent FESz group was not able to classify better than chance, however, accurately classified 67.5% of the FESL but only 28% of their controls, Pearson  $X(1,79) = 0.17$ ,  $P = 0.63$ .

#### 3.2.2. Stage 2

**3.2.2.1. N100, P200 difference scores.** Stepwise discriminant analysis with difference scores based on within group analysis (Table 2) were able to correctly identify 77.5% of the CSz group and 70% of the controls, Wilk's  $A(2,78) = 0.64$ ,  $\chi^2 = 34.66$ ,  $P < 0.001$ , using Nt after minus target P200 amplitude (0.53) and Nt before minus target P200 latency (0.68). Similarly, 75% of the FESz group and 66.7% of their control group were able to be classified using the same two variables, Nt after minus target P200 amplitude (0.98) and Nt before minus target P200 latency (-0.68).

### 3.3. Reaction time

Both the CSz group (mean = 0.41 s, SD = 0.11) and the FESz group (mean = 0.35 s, SD = 0.01), showed significantly slower reaction times ( $df = 78$ ,  $P < 0.001$  and  $df = 78$ ,  $P < 0.01$ , respectively) than their normal controls (mean = 0.35 s, SD = 0.01; mean = 0.31 s, SD = 0.04). There were no significant differences between the CSz

and FESz groups, or the two control groups. Control groups averaged 99.8% (1) and 99.9% (2) accuracy, with the CSz group 93% and the FESz 96.2% accuracy.

#### 4. Discussion

These results suggest that abnormalities in ERPs to both target and non-target stimuli are evident at the onset of schizophrenia, trait-like and not due to secondary effects of chronic morbidity, neuroleptics or institutionalisation. For both the CSz and FESz groups the traditional averaged ERP to target stimuli showed decreased N100, N200 and P300 amplitudes and increased P200 amplitude when compared with their controls. The reduced N100, N200 and P300 amplitudes are consistent with the previous ERP studies with schizophrenia (Ogura et al., 1991; Boutros et al., 1997; Brown et al., 2000) and with the reduced P300 findings in the FESz studies (Salisbury et al., 1998; Hirayasu et al., 1998). Previous target P200 amplitude findings have been mixed, however, our increased P200 amplitude finding replicates that of Ogura et al. (1991) in an unmedicated sample. P200 amplitude has been reported to reflect aspects of decision making or stimulus encoding (McCarley et al., 1991).

There were some differences between the CSz and FESz groups and their respective controls. While amplitude disturbances were common to both groups, latency deficits were specific to the chronic group who showed delayed latencies for P200 and N200 components to targets and earlier P200 latency for non-targets, with the FESz group showing no significant difference in latency from their control group. One possible explanation for this pattern of results could be that the amplitude deficits observed manifest consequences of the disease itself, whereas the course of illness may have effects on speed of processing specific types of information. Considering latency impairments seen in CSz were restricted to targets, this would suggest that processing delays affected stimulus changes (infrequent target stimuli) but not non-target stimuli. In addition, the reduced P200 amplitude to Nt after stimuli found in the FESz was not found in the CSz group. However, the degree of similarity between the CSz and FESz groups is emphasised by their direct comparison, where no significant differences in ERP components remained after covarying for age. Interestingly, the P300 decrement with age observed in comparisons between the Normal control groups was not observed in comparisons between CSz and FESz groups. Among other interpretive possibilities, this pattern of results may indicate that P300 amplitude deficits may be a more sensitive index early in the schizophrenic process, and such a pattern of results was observed in the dfa where the P300 amplitude deficits was one of only two valuable discriminators for FESz, whereas it was significant, but did not rate that highly for the CSz group.

The disturbance in information processing is also elucidated by a comparison of within group analysis, where the

controls have a pattern of significant differences between targets and non-targets (smaller earlier P200 to targets vs. increased delayed P200 to non-targets) while both CSz and FESz groups failed to show this pattern (see Fig. 2 and Table 2). In the CSz group P200 amplitude and latency did not vary significantly between target and non-target stimuli and in the FESz, while they do show a shift in P200 latency between target and non-target stimuli, the P200 amplitude either does not vary significantly (Fz, Cz) or is increased (Pz) (i.e. varies in the opposite direction to the controls). It appears that the P200 amplitude and latency shift between targets and non-targets found in the controls results mainly from the overlap with the N200 components in ERPs to target stimuli. Thus the large P200 amplitude component normally elicited by non-target stimuli is foreshortened by the negative shift for the N200 component in ERPs elicited to target stimuli. It is possible that this does not occur to the same extent in the CSz and FESz groups because their N200 and P300 components are reduced compared with controls and so the N200 overlap is not so prominent in the P200 component which would contribute to the larger P200 amplitude to targets found in the CSz group when compared with controls. We intend to use a new single trial method developed by our lab (Melkonian et al., 2001) to tease out the overlapping components to clarify this and investigate among other questions, whether any P200 differences remain when the effects of the overlap are removed.

The N100 component is correlated with specific aspects of stimulus features (Pritchard, 1986; Naatanen and Picton, 1987) but may also reflect attention, being generally larger with greater attentional requirements (Maclea et al., 1975) and is also affected by non-specific arousal (Rockstroh et al., 1994). We found that, in addition to the overall reduction of N100 amplitude in the CSz and FESz groups, they also failed to show the distinct pattern of Nt before > Nt after N100 amplitude found in the control groups. As the stimulus features of the Nt after and Nt before stimuli are identical, it is possible that the reduction in N100 amplitude to Nt after stimuli found in normal controls, but not in patient participants, could be due to temporal recovery (as the Nt after stimuli follow a target that requires a cognitive and motor response) or to a reduced attentional requirement for Nt after stimuli due to expectancy (the expectancy may occur because, in this paradigm, a target stimuli is always followed by a non-target). These two possibilities will be further explored by averaging blocks of trials across the paradigm and single trial analysis to see if the reduction in Nt after N100 is consistent across the paradigm which would indicate temporal recovery, or if decreases occur across the course of the paradigm indicating the development of expectancy.

The patient group's diminished discrimination between targets and non-targets (and also between Nt before and Nt after) suggests that they are less flexible in differentiating and processing target and inhibiting non-target information than controls. This pattern of findings is consistent with

Gray's (1998) model in which 'misattributions' in the match/mismatching of target: non-target information is proposed to underlie the core positive symptoms in schizophrenia. A failure to develop an expectancy that a non-target would follow a target could be further evidence of this dysfunction and may be viewed, among other possibilities, as a disturbance of implicit memory.

Compared with the P300 component, which has been the focus of schizophrenia research, the N100, P200 components acquired in response to both targets and non-targets gave a more accurate classification for both the CSz group (improved from 70 to 85%) and the FESz group (improved from 72.5 to 77.5%). Thus, the current study's emphasis on extending ERP investigations to components other than P300 is vindicated. The combination of N100 and P200 components derived from Nt before stimuli and P300 components derived from target stimuli produce the best classification rates for the CSz group, whereas the best classification rates for the FESz group involved the combination of N100 and P300 amplitudes both derived from target stimuli.

Perceptual abnormalities are an early sign of the onset of psychosis (Chapman, 1966) and the development of an investigational means to assess this would be of great importance. With the current emphasis on first episode psychosis treatment on early identification and active treatment of young people at risk (McGlashan, 2000; McGlashan, 2001), an investigational means to help highlight risk prior to a psychotic episode and track treatment progress is important. For these purposes and to avoid unnecessary use of antipsychotic medication it is imperative to be able to correctly differentiate FESz from normal and other non-psychotic controls. Forty-two and a half percent of the controls would have been falsely classified as FESz using the P300 component vs. 25% using the N100 and P200 components to both target and non-target stimuli.

Some final caveats should be mentioned here. In this paper we limited our participants to those with a diagnosis of FESz (for comparison with the chronic group and specificity to schizophrenia), we still need to analyse data we have collected from first episode psychosis (FEP) patients who attracted diagnoses other than FESz to see if these findings are applicable across FEP. In addition, our data indicate that these disturbances are present at the time of the first episode, it is yet to be determined if they are present prior to the first episode and also if they are specific to psychosis when compared with other young clinical groups (e.g. attention deficit hyperactivity disorder — ADHD).

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## APPENDIX 3

### Statistical summaries for the four studies contained in this thesis.

1	Study 1 .....	3
1.1	N100 amplitude.....	3
1.2	N100 latency .....	3
1.3	P200 amplitude .....	4
1.4	P200 latency.....	4
1.5	N200 amplitude.....	5
1.6	N200 Latency.....	5
1.7	P300 amplitude .....	5
1.8	P300 latency.....	5
2	Study 2 .....	6
2.1	Midline Site.....	6
2.1.1	N100 amplitude.....	6
2.1.2	N100 latency .....	7
2.1.3	P200 amplitude .....	8
2.1.4	P200 latency.....	10
2.1.5	N200 amplitude.....	11
2.1.6	N200 latency .....	13
2.1.7	P300 amplitude .....	13
2.1.8	P300 latency.....	14
2.1.9	Age-ERP correlations.....	14
2.1.10	Symptom-ERP correlations.....	15
2.2	Topography .....	16
2.2.1	N100 amplitude.....	16
2.2.2	N100 latency .....	17
2.2.3	P200 amplitude .....	18
2.2.4	P200 latency.....	19
2.2.5	N200 and P300 components .....	20
3	Study 3 .....	21
3.1	DR.....	21
3.1.1	P300 Amplitude .....	21
3.1.2	P300 latency.....	22
3.1.3	RT .....	22
3.2	DA.....	22
3.2.1	P300 amplitude .....	22
3.2.2	P300 Latency .....	23
3.2.3	RT .....	23
3.3	Continuing (NN, TT) and discontinuing (TN, NT) series. ....	24
3.3.1	P300 amplitude .....	24
3.3.2	N100 amplitude.....	25
4	Study 4 .....	26
4.1.1	N100 amplitude.....	26
4.1.2	N100 Latency.....	27
4.1.3	P200 amplitude .....	28
4.1.4	P200 Latency .....	29

		2
4.1.5	N200 amplitude.....	30
4.1.6	N200 latency .....	30
4.1.7	P300 amplitude .....	31
4.1.8	P300 latency.....	31

# 1 STUDY 1

## 1.1 N100 amplitude

		Contrasts	Sz vs Control	
Df (1,78)			F	p
Group			30.83	0.000
Group X Stimulus	T vs NT		1.74	0.191
Group X Site		Cz vs Fz & Pz	19.31	0.000
		Fz vs Pz	0.53	0.468
Group X Stimulus X Site	T vs NT	Cz vs Fz & Pz	1.29	0.259
		Fz vs Pz	0.67	0.416
Stimulus	T vs NT		53.09	0.000
Stimulus X Site	T vs NT	Cz vs Fz & Pz	25.02	0.000
		Fz vs Pz	22.45	0.000
Site		Cz vs Fz & Pz	259.51	0.000
		Fz vs Pz	130.56	0.000

## 1.2 N100 latency

		Contrasts	Sz vs Control	
Df (1,78)			F	p
Group			2.88772	0.093242
Group X Stimulus	T vs NT		9.761876	0.002502
Group X Site		Cz vs Fz & Pz	0.087288	0.768439
		Fz vs Pz	1.587763	0.211403
Group X Stimulus X Site	T vs NT	Cz vs Fz & Pz	0.364497	0.547771
		Fz vs Pz	0.002516	0.960123
Stimulus	T vs NT		2.90436	0.092321
Stimulus X Site	T vs NT	Cz vs Fz & Pz	2.108543	0.150489
		Fz vs Pz	16.19872	0.000131
Site		Cz vs Fz & Pz	2.155114	0.146117
		Fz vs Pz	3.160987	0.079315

### 1.3 P200 amplitude

	Contrasts	Sz vs Control	
		F	<i>p</i>
Df (1,78)			
Group		5.25659	0.024559
Group X Stimulus	T vs NT	19.80	0.0000
Group X Site	Cz vs Fz & Pz	10.00	0.0022
	Fz vs Pz	0.83	0.3653
Group X Stimulus X Site	T vs NT	22.69	0.0000
	Fz vs Pz	0.57	0.4529
Stimulus	T vs NT	16.13	0.0001
Stimulus X Site	T vs NT	39.01	0.0000
	Fz vs Pz	9.96	0.0023
Site	Cz vs Fz & Pz	34.37	0.0000
	Fz vs Pz	2.52	0.1165

### 1.4 P200 latency

	Contrasts	Sz vs Control	
		F	<i>p</i>
Df (1,78)			
Group		5.16	0.026
Group X Stimulus	T vs NT	18.77	0.000
Group X Site	Cz vs Fz & Pz	0.10	0.749
	Fz vs Pz	0.42	0.521
Group X Stimulus X Site	T vs NT	3.32	0.072
	Fz vs Pz	0.34	0.559
Stimulus	T vs NT	53.24	0.000
Stimulus X Site	T vs NT	1.69	0.197
	Fz vs Pz	0.11	0.736
Site	Cz vs Fz & Pz	2.15	0.146
	Fz vs Pz	6.34	0.014

## 1.5 N200 amplitude

Df (1,78)	Contrasts	Sz vs Control	
		F	<i>p</i>
Group		6.88	0.010
Group X Site	Cz vs Fz & Pz	18.97	0.000
	Fz vs Pz	4.29	0.042
Site	Cz vs Fz & Pz	18.12	0.000
	Fz vs Pz	39.52	0.000

## 1.6 N200 Latency

Df (1,78)	Contrasts	Sz vs Control	
		F	<i>p</i>
Group		7.18	0.009
Group X Site	Cz vs Fz & Pz	0.01	0.919
	Fz vs Pz	1.82	0.181
Site	Cz vs Fz & Pz	0.11	0.742
	Fz vs Pz	7.55	0.007

## 1.7 P300 amplitude

Df (1,77)	Contrasts	Sz vs Control	
		F	<i>p</i>
Group		4.44	0.038
Group X Site	Cz vs Fz & Pz	13.03	0.001
	Fz vs Pz	2.64	0.108
Site	Cz vs Fz & Pz	7.87	0.006
	Fz vs Pz	119.41	0.000

## 1.8 P300 latency

Df (1,77)	Contrasts	Sz vs Control	
		F	<i>p</i>
Group		1.83	0.181
Group X Site	Cz vs Fz & Pz	0.88	0.351
	Fz vs Pz	2.75	0.101
Site	Cz vs Fz & Pz	5.68	0.020
	Fz vs Pz	11.68	0.001

## 2 STUDY 2

### 2.1 Midline Site

#### 2.1.1 N100 amplitude

Df (1,76) Group	Contrasts		Csz vs controls		FESz vs controls	
	Stimulus	Site	F	p	F	p
Group			30.08	0.000	6.45	0.013
Group X Stimulus	T vs NTs		1.33	0.253	9.61	0.003
	T-1 vs T+1		6.14	0.015	1.95	0.167
Group X Site		Cz vs Fz & Pz	15.22	0.000	10.98	0.001
		Fz vs Pz	1.57	0.214	3.93	0.051
Group X Stimulus X Site	T vs NTs	Cz vs Fz & Pz	12.76	0.001	3.27	0.074
		Fz vs Pz	0.72	0.398	31.32	0.000
	T-1 vs T+1	Cz vs Fz & Pz	11.44	0.001	1.11	0.295
		Fz vs Pz	0.01	0.905	0.90	0.345
Stimulus	T vs NTs		15.78	0.000	15.37	0.000
	T-1 vs T+1		1.60	0.210	8.96	0.004
Stimulus X Site	T vs NTs	Cz vs Fz & Pz	24.37	0.000	13.04	0.001
		Fz vs Pz	9.84	0.002	19.72	0.000
	T-1 vs T+1	Cz vs Fz & Pz	37.20	0.000	13.37	0.000
		Fz vs Pz	0.29	0.595	2.18	0.144
Site		Cz vs Fz & Pz	140.28	0.000	25.86	0.000
		Fz vs Pz	123.65	0.000	74.71	0.000
Gender			5.57	0.021	3.90	0.052
Group X Gender			2.78	0.100	0.73	0.396
Group X Gender X Stimulus	T vs NTs		0.07	0.792	0.11	0.743
	T-1 vs T+1		0.31	0.578	0.01	0.915
Group X Gender X Site		Cz vs Fz & Pz	0.10	0.749	0.01	0.930
		Fz vs Pz	0.07	0.787	1.32	0.254
Grp X Gender X Stim X Site	T vs NTs	Cz vs Fz & Pz	0.00	0.967	3.12	0.081
		Fz vs Pz	0.02	0.886	0.31	0.579
	T-1 vs T+1	Cz vs Fz & Pz	0.09	0.762	0.00	0.948
		Fz vs Pz	0.31	0.579	0.01	0.932
Gender X Stimulus	T vs NTs		1.07	0.305	0.22	0.643
	T-1 vs T+1		0.43	0.515	1.47	0.230
Gender X Stimulus X Site	T vs NTs	Cz vs Fz & Pz	1.17	0.283	1.09	0.299
		Fz vs Pz	0.00	0.970	1.62	0.208
	T-1 vs T+1	Cz vs Fz & Pz	8.57	0.005	0.18	0.673
		Fz vs Pz	0.07	0.787	0.00	0.999
Gender X Site		Cz vs Fz & Pz	0.00	0.957	0.08	0.776
		Fz vs Pz	2.34	0.130	0.06	0.814

### 2.1.2 N100 amplitude/age correlation

	control		Schizophrenia	
	r	p	r	p
T-1 N100 amplitude	-0.336	0.002	-0.114	0.316
T N100 amplitude	-0.287	0.010	-0.337	0.002
T+1 N100 amplitude	-0.238	0.034	-0.200	0.076

### 2.1.3 N100 amplitude? Symptom correlation

		CSz		FESz	
		r	p	r	p
T-1CzN100 amplitude	Reality distortion	0.12	0.47	0.26	0.14
	Psychomotor poverty	0.07	0.7	0.29	0.09
	Disorganisation	0.42	0.01	0.4	0.02
TCzN100 amplitude	Reality distortion	0.24	0.16	0.02	0.91
	Psychomotor poverty	0.07	0.68	0.13	0.46
	Disorganisation	0.36	0.03	0.22	0.22
T+1CzN100 amplitude	Reality distortion	0.17	0.3	-0.11	0.53
	Psychomotor poverty	0.16	0.36	0.15	0.4
	Disorganisation	0.36	0.03	0.32	0.06

### 2.1.4 N100 latency

			Contrasts		CSz vs control		FESz vs control	
Df (1,76)	Stimulus	Site			F	Sig.	F	Sig.
Group					0.38	0.542	1.86	0.18
Group X Stimulus	T vs NTs				2.79	0.099	0.17	0.68
	T-1 vs T+1				2.65	0.108	0.65	0.42
Group X Site		Cz vs Fz & Pz			5.27	0.025	0.47	0.49
		Fz vs Pz			0.26	0.610	0.09	0.77
Group X Stimulus X Site	T vs NTs	Cz vs Fz & Pz			4.05	0.048	0.10	0.75
		Fz vs Pz			0.21	0.651	3.01	0.09
	T-1 vs T+1	Cz vs Fz & Pz			0.55	0.459	0.78	0.38
		Fz vs Pz			0.42	0.519	0.18	0.67
Stimulus	T vs NTs				0.01	0.937	0.03	0.86
	T-1 vs T+1				2.89	0.093	2.26	0.14
Stimulus X Site	T vs NTs	Cz vs Fz & Pz			1.47	0.229	0.15	0.70
		Fz vs Pz			2.18	0.144	0.70	0.41
	T-1 vs T+1	Cz vs Fz & Pz			1.82	0.181	0.81	0.37
		Fz vs Pz			0.16	0.691	1.17	0.28



Site		Cz vs Fz & Pz	1.05	0.310	0.91	0.34
		Fz vs Pz	16.95	0.000	26.76	0.0000
Gender			5.39	0.023	0.55	0.46
Group X Gender			0.02	0.885	0.46	0.50
Group X Gender X Stimulus	T vs NTs		0.83	0.365	0.80	0.37
	T-1 vs T+1		0.23	0.634	0.46	0.50
Group X Gender X Site		Cz vs Fz & Pz	3.02	0.086	0.72	0.40
		Fz vs Pz	0.11	0.739	0.48	0.49
Group X Gender X Stimulus X Site	T vs NTs	Cz vs Fz & Pz	0.03	0.859	0.02	0.88
		Fz vs Pz	0.12	0.732	1.70	0.20
	T-1 vs T+1	Cz vs Fz & Pz	0.19	0.661	0.14	0.71
		Fz vs Pz	1.51	0.223	0.01	0.90
Gender X Stimulus	T vs NTs		7.46	0.008	0.55	0.46
	T-1 vs T+1		0.09	0.766	1.36	0.25
Gender X Stimulus X Site	T vs NTs	Cz vs Fz & Pz	4.05	0.048	1.15	0.29
		Fz vs Pz	0.90	0.345	0.00	0.98
	T-1 vs T+1	Cz vs Fz & Pz	0.47	0.497	0.23	0.63
		Fz vs Pz	4.96	0.029	0.00	0.98
Gender X Site		Cz vs Fz & Pz	3.15	0.080	0.48	0.49
		Fz vs Pz	1.25	0.268	0.72	0.40

### 2.1.5 N100 latency/age correlations

	control		Schizophrenia	
	r	p	r	p
T-1 N100 latency	-0.08	0.5	0.07	0.51
T N100 latency	0.07	0.56	0.18	0.11
T+1 N100 latency	-0.16	0.16	0.1	0.37

### 2.1.6 N100 latency/symptom correlations

		CSz		FESz	
		<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
T-1CzN100 latency	Reality distortion	0.01	0.96	-0.13	0.48
	Psychomotor poverty	0.02	0.89	0.08	0.66
	Disorganisation	0.12	0.49	0.13	0.46
TCzN100 latency	Reality distortion	0.01	0.93	0.15	0.4
	Psychomotor poverty	-0.06	0.73	0.01	0.94
	Disorganisation	0.05	0.76	0.28	0.12
T+1CzN100 latency	Reality distortion	-0.01	0.96	-0.19	0.28
	Psychomotor poverty	-0.1	0.57	-0.01	0.94
	Disorganisation	-0.09	0.6	-0.12	0.49

### 2.1.7 P200 amplitude

			Contrasts		CSz vs. control		FESz vs. control	
Df (1,76)	Stimulus	Site			<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Group					12.21	0.001	0.18	0.675
Group X Stimulus	T vs NTs				24.98	0.000	5.45	0.022
	T-1 vs T+1				0.48	0.489	3.90	0.052
Group X Site		Cz vs Fz & Pz			3.62	0.061	2.62	0.109
		Fz vs Pz			0.36	0.548	4.36	0.040
Group X Stimulus X Site	T vs NTs	Cz vs Fz & Pz			18.87	0.000	0.67	0.415
		Fz vs Pz			3.60	0.062	3.98	0.050
	T-1 vs T+1	Cz vs Fz & Pz			0.42	0.519	0.97	0.328
		Fz vs Pz			0.57	0.452	0.01	0.935
Stimulus	T vs NTs				12.35	0.001	0.88	0.352
	T-1 vs T+1				2.26	0.137	0.48	0.493
Stimulus X Site	T vs NTs	Cz vs Fz & Pz			25.17	0.000	3.81	0.055
		Fz vs Pz			7.54	0.008	12.78	0.001
	T-1 vs T+1	Cz vs Fz & Pz			3.62	0.061	0.53	0.471
		Fz vs Pz			0.16	0.693	5.51	0.022
Site		Cz vs Fz & Pz			57.16	0.000	47.79	0.000
		Fz vs Pz			4.11	0.046	33.63	0.000
Gender					1.94	0.168	0.50	0.481
Group X Gender					0.19	0.666	0.79	0.376
Group X Gender X Stimulus	T vs NTs				0.63	0.431	3.10	0.082
	T-1 vs T+1				0.27	0.605	0.45	0.503
Group X Gender X Stimulus X Site	T vs NTs	Cz vs Fz & Pz			1.06	0.307	0.02	0.883
		Fz vs Pz			2.12	0.149	0.01	0.934
	T-1 vs T+1	Cz vs Fz & Pz			0.55	0.459	0.04	0.836

Group X Gender X Site		Fz vs Pz	2.18	0.144	0.00	0.949
		Cz vs Fz & Pz	0.38	0.537	0.03	0.868
		Fz vs Pz	1.43	0.235	0.46	0.498
Stimulus X Gender	T vs NTs		8.83	0.004	1.06	0.306
	T-1 vs T+1		0.90	0.346	0.00	0.982
Gender X Stimulus X Site	T vs NTs	Cz vs Fz & Pz	4.73	0.033	1.65	0.203
		Fz vs Pz	0.11	0.736	0.10	0.753
	T-1 vs T+1	Cz vs Fz & Pz	8.32	0.005	0.53	0.469
Gender X Site		Fz vs Pz	0.12	0.726	0.07	0.798
		Cz vs Fz & Pz	1.91	0.171	0.06	0.805
		Fz vs Pz	3.54	0.064	0.07	0.788

### 2.1.8 P200 amplitude/age correlations

	control		Schizophrenia	
	r	p	r	p
T-1 P200 amplitude	0.11	0.33	0.22	0.05
T P200 amplitude	-0.16	0.16	0.14	0.2
T+1 P200 amplitude	0.07	0.56	0.24	0.03

### 2.1.9 P200 amplitude/ symptom correlations

		CSz		FESz	
		r	p	r	p
T-1CzP200 amplitude	Reality distortion	-0.14	0.42	0.01	0.96
	Psychomotor poverty	-0.21	0.2	0.09	0.59
	Disorganisation	-0.02	0.91	0.06	0.74
TCzP200 amplitude	Reality distortion	0.14	0.39	-0.02	0.93
	Psychomotor poverty	0.17	0.31	-0.1	0.58
	Disorganisation	0.2	0.23	-0.03	0.86
T+1CzP200 amplitude	Reality distortion	0.09	0.6	-0.15	0.39
	Psychomotor poverty	0.25	0.14	-0.29	0.09
	Disorganisation	0.05	0.77	-0.12	0.5

### 2.1.10 P200 latency

Df(1,76)	Contrasts		CSz vs control		FESz vs control	
	Stimulus	Site	F	Sig.	F	Sig.
Group			5.62	0.020	0.00	0.994
Group X Stimulus	T vs NTs		40.50	0.000	3.72	0.058
	T-1 vs T+1		0.02	0.886	0.73	0.395
Group X Site		Cz vs Fz & Pz	0.04	0.845	0.29	0.590
		Fz vs Pz	0.74	0.394	0.03	0.871

Group X Stimulus X Site	T vs NTs	Cz vs Fz & Pz	3.88	0.053	0.02	0.881
		Fz vs Pz	0.36	0.548	1.00	0.321
	T-1 vs T+1	Cz vs Fz & Pz	0.90	0.345	0.01	0.936
		Fz vs Pz	2.09	0.153	0.18	0.677
Stimulus	T vs NTs		65.18	0.000	32.95	0.000
	T-1 vs T+1		0.01	0.926	1.76	0.189
Stimulus X Site	T vs NTs	Cz vs Fz & Pz	15.51	0.000	2.28	0.135
		Fz vs Pz	0.09	0.762	4.30	0.042
	T-1 vs T+1	Cz vs Fz & Pz	0.08	0.784	0.00	0.959
		Fz vs Pz	3.43	0.068	1.43	0.236
Site	Cz vs Fz & Pz		0.02	0.892	0.62	0.433
	Fz vs Pz		4.37	0.040	2.45	0.121
Gender			0.50	0.482	2.45	0.121
Group X Gender			0.14	0.707	0.81	0.372
Group X Gender X Stimulus	T vs NTs		4.67	0.034	0.30	0.586
	T-1 vs T+1		0.54	0.465	0.10	0.755
Group X Gender X Stimulus X Site	T vs NTs	Cz vs Fz & Pz	5.54	0.021	5.22	0.025
		Fz vs Pz	2.55	0.114	2.24	0.139
	T-1 vs T+1	Cz vs Fz & Pz	2.42	0.124	0.21	0.646
		Fz vs Pz	1.81	0.183	1.56	0.216
Group X Gender X Site	Cz vs Fz & Pz		3.64	0.060	0.06	0.806
	Fz vs Pz		4.32	0.041	0.46	0.498
Stimulus X Gender	T vs NTs		0.42	0.517	1.74	0.191
	T-1 vs T+1		0.04	0.847	4.15	0.045
Gender X Stimulus X Site	T vs NTs	Cz vs Fz & Pz	0.00	0.960	0.17	0.679
		Fz vs Pz	0.04	0.848	0.22	0.638
	T-1 vs T+1	Cz vs Fz & Pz	0.05	0.820	0.84	0.362
		Fz vs Pz	0.94	0.336	0.94	0.336
Gender X Site	Cz vs Fz & Pz		1.03	0.314	0.66	0.419
	Fz vs Pz		1.13	0.291	1.04	0.312

### 2.1.11 P200 latency/age correlation

	control		Schizophrenia	
	r	p	r	p
T-1 P200 latency	0.32		0	0.17
T P200 latency	-0.07	0.53	0.23	0.04

T+1 P200 latency	0.27	0.01	0.12	0.31
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### 2.1.12 P200 latency/symptom correlation

		CSz		FESz	
		<i>r</i>	p	<i>r</i>	p
T-1CzN100 latency	Reality distortion	-0.33	0.05	-0.26	0.14
	Psychomotor poverty	-0.2	0.23	0.09	0.61
	Disorganisation	-0.17	0.32	0.02	0.91
TCzN100 latency	Reality distortion	-0.1	0.55	0.12	0.5
	Psychomotor poverty	-0.13	0.44	0.14	0.45
	Disorganisation	-0.13	0.43	0.1	0.59
T+1CzN100 latency	Reality distortion	0.08	0.66	0.02	0.89
	Psychomotor poverty	-0.12	0.49	0	0.99
	Disorganisation	0.15	0.37	0.02	0.9

### 2.1.13 N200 amplitude

		CSz vs control		FESz vs control	
Df (1,76)CSz, (1,75) FESz	Contrasts	F	Sig.	F	Sig.
Group		17.98	0.0001	2.52	0.1170
Group X Site	Cz vs Fz & Pz	19.80	0.0000	0.32	0.5742
	Fz vs Pz	0.86	0.3576	10.58	0.0017
Site	Cz vs Fz & Pz	20.90	0.0000	10.73	0.0016
	Fz vs Pz	60.71	0.0000	132.95	0.0000
Gender		7.60	0.0073	0.00	0.9531
Group X Gender		0.49	0.4859	0.14	0.7135
Group X Gender X Site	Cz vs Fz & Pz	0.06	0.8149	0.39	0.5350
	Fz vs Pz	4.39	0.0396	0.71	0.4026
Gender X Site	Cz vs Fz & Pz	0.42	0.5184	0.06	0.8101
	Fz vs Pz	2.33	0.1309	1.07	0.3033

### 2.1.14 N200 amplitude/ age correlations

### 2.1.15 N200 amplitude/ symptom correlations

### 2.1.16 N200 latency

Df (1,76)CSz, (1,75)FESz	Contrasts	CSz vs. controls		FESz vs. controls	
		F	Sig.	F	Sig.
Group		5.25	0.0248	2.49	0.1191
Group X Site	Cz vs Fz & Pz	11.89	0.0009	0.10	0.7575
	Fz vs Pz	0.01	0.9355	0.00	0.9956
Site	Cz vs Fz & Pz	4.52	0.0368	2.11	0.1504
	Fz vs Pz	152.75	0.0000	24.20	0.0000
Gender		2.78	0.0997	1.03	0.3136
Group X Gender		0.07	0.7878	0.20	0.6556
Group X Gender X Site	Cz vs Fz & Pz	0.40	0.5301	0.47	0.4949
	Fz vs Pz	2.90	0.0927	0.23	0.6357
Gender X Site	Cz vs Fz & Pz	0.29	0.5895	1.44	0.2337
	Fz vs Pz	0.00	0.9609	0.08	0.7817

### 2.1.17 P300 amplitude

DF (1,76)	Contrasts	CSz vs control		FESz vs control	
		F	p	F	p
Group		5.25	0.0248	5.31	0.0240
Group X Site	Cz vs Fz & Pz	11.89	0.0009	0.47	0.4941
	Fz vs Pz	0.01	0.9355	4.38	0.0396
Site	Cz vs Fz & Pz	4.52	0.0368	1.83	0.1801
	Fz vs Pz	152.75	0.0000	148.54	0.0000
Gender		2.78	0.0997	0.04	0.8451
Group X Gender		0.07	0.7878	0.20	0.6550
Group X Gender X Site	Cz vs Fz & Pz	0.40	0.5301	0.01	0.9035
	Fz vs Pz	2.90	0.0927	1.15	0.2868
Gender X Site	Cz vs Fz & Pz	0.29	0.5895	0.01	0.9285

Fz vs Pz	0.00	0.9609	0.92	0.3403
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### 2.1.18 P300 latency

		CSz vs control		FESz vs control	
DF (1,76)	Contrasts				
Group		0.18	0.6705	0.41	0.526
Group X Site	Cz vs Fz & Pz	3.18	0.0786	1.72	0.194
	Fz vs Pz	0.05	0.8317	0.76	0.387
Site	Cz vs Fz & Pz	14.71	0.0003	1.24	0.269
	Fz vs Pz	10.15	0.0021	1.25	0.268
Gender		0.61	0.4367	0.01	0.936
Group X Gender		0.27	0.6100	0.02	0.883
Group X Gender X Site	Cz vs Fz & Pz	1.15	0.2875	1.71	0.194
	Fz vs Pz	0.90	0.3447	1.93	0.169
Gender X Site	Cz vs Fz & Pz	0.08	0.7738	0.01	0.915
	Fz vs Pz	0.48	0.4922	0.49	0.487

### 2.1.19 Age/ERP correlations

		Combined control groups	Combined Schizophrenia groups
		AGE	AGE
T-1CzN100 amplitude	Pearson Correlation	-0.34	-0.11
	Sig. (2-tailed)	0.00	0.32
T-1CzN100 latency	Pearson Correlation	-0.08	0.07
	Sig. (2-tailed)	0.50	0.51
T-1CzP200 amplitude	Pearson Correlation	0.11	0.22
	Sig. (2-tailed)	0.33	0.05
T-1CzP200 latency	Pearson Correlation	0.32	-0.15
	Sig. (2-tailed)	0.00	0.17
TCzN100 amplitude	Pearson Correlation	-0.29	-0.34
	Sig. (2-tailed)	0.01	0.00
TCzN100 latency	Pearson Correlation	0.07	0.18
	Sig. (2-tailed)	0.56	0.11
TCzP200 amplitude	Pearson Correlation	-0.16	0.14
	Sig. (2-tailed)	0.16	0.20
TCzP200 latency	Pearson Correlation	-0.07	0.23

	Sig. (2-tailed	0.53	0.04
TFzN200 amplitude	Pearson Correlation	0.44	0.21
	Sig. (2-tailed	0.00	0.06
TFzN200 latency	Pearson Correlation	0.01	0.18
	Sig. (2-tailed	0.91	0.10
TPzP300 amplitude	Pearson Correlation	-0.39	-0.22
	Sig. (2-tailed	0.00	0.05
TPzP300 latency	Pearson Correlation	0.20	0.02
	Sig. (2-tailed	0.07	0.86
T+1CzN100 amplitude	Pearson Correlation	-0.24	-0.20
	Sig. (2-tailed	0.03	0.08
T+1CzN100 latency	Pearson Correlation	-0.16	0.10
	Sig. (2-tailed	0.16	0.37
T+1CzP200 amplitude	Pearson Correlation	0.07	0.24
	Sig. (2-tailed	0.56	0.03
T+1CzP200 latency	Pearson Correlation	0.27	0.12
	Sig. (2-tailed	0.01	0.31

### 2.1.20 Symptom/ERP correlations

		chronic schizophrenia			first episode schizophrenia			
		RD	PP	D	RD	PP	D	
T-1CzN100 amplitude	Pearson Correlation	0.12	0.07	0.42	0.26	0.29	0.40	
	Sig. (2-tailed)	0.47	0.70	0.01	0.14	0.09	0.02	
T-1CzN100 latency	Pearson Correlation	0.01	0.02	0.12	-0.13	0.08	0.13	
	Sig. (2-tailed)	0.96	0.89	0.49	0.48	0.66	0.46	
T-1CzP200 amplitude	Pearson Correlation	-0.14	-0.21	-0.02	0.01	0.09	0.06	
	Sig. (2-tailed)	0.42	0.20	0.91	0.96	0.59	0.74	
T-1CzP200 latency	Pearson Correlation	-0.33	-0.20	-0.17	-0.26	0.09	0.02	
	Sig. (2-tailed)	0.05	0.23	0.32	0.14	0.61	0.91	
TCzN100 amplitude	Pearson Correlation	0.24	0.07	0.36	0.02	0.13	0.22	
	Sig. (2-tailed)	0.16	0.68	0.03	0.91	0.46	0.22	
TCzN100 latency	Pearson Correlation	0.01	-0.06	0.05	0.15	0.01	0.28	
	Sig. (2-tailed)	0.93	0.73	0.76	0.40	0.94	0.12	
TCzP200 amplitude	Pearson Correlation	0.14	0.17	0.20	-0.02	-0.10	-0.03	
	Sig. (2-tailed)	0.39	0.31	0.23	0.93	0.58	0.86	



TCzP200 latency	Pearson Correlation	-0.10	-0.13	-0.13	0.12	0.14	0.10
	Sig. (2-tailed)	0.55	0.44	0.43	0.50	0.45	0.59
TFzN200 amplitude	Pearson Correlation	0.22	-0.08	-0.11	-0.07	-0.03	-0.02
	Sig. (2-tailed)	0.20	0.64	0.52	0.69	0.84	0.92
TFzN200 latency	Pearson Correlation	0.03	-0.01	0.19	-0.03	0.00	0.07
	Sig. (2-tailed)	0.86	0.97	0.25	0.88	0.98	0.68
TPzP300 amplitude	Pearson Correlation	0.19	0.07	0.15	-0.16	-0.20	-0.26
	Sig. (2-tailed)	0.25	0.66	0.37	0.37	0.26	0.14
TPzP300 latency	Pearson Correlation	-0.09	-0.12	0.05	-0.07	-0.10	0.01
	Sig. (2-tailed)	0.58	0.47	0.77	0.70	0.56	0.95
T+1CzN100 amplitude	Pearson Correlation	0.17	0.16	0.36	-0.11	0.15	0.32
	Sig. (2-tailed)	0.30	0.36	0.03	0.53	0.40	0.06
T+1CzN100 latency	Pearson Correlation	-0.01	-0.10	-0.09	-0.19	-0.01	-0.12
	Sig. (2-tailed)	0.96	0.57	0.60	0.28	0.94	0.49
T+1CzP200 amplitude	Pearson Correlation	0.09	0.25	0.05	-0.15	-0.29	-0.12
	Sig. (2-tailed)	0.60	0.14	0.77	0.39	0.09	0.50
T+1CzP200 latency	Pearson Correlation	0.08	-0.12	0.15	0.02	0.00	0.02
	Sig. (2-tailed)	0.66	0.49	0.37	0.89	0.99	0.90

## 2.2 Topography

### 2.2.1 N100 amplitude

#### 2.2.1.1 Hemisphere (left-right)

Df (1,60) CSz, (1,59) FESz	Stimulus	Hemisphere	Chronic Sz		FESz	
			<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Group			21.101	0.000	12.970	0.001
Group X Hemisphere		L vs R	1.696	0.198	0.812	0.371
Group X Stimulus	T vs NTs		0.687	0.411	17.313	0.000
	T-1 vs T+1		1.098	0.299	0.992	0.323
Group X Hem X Stim	T vs NTs	L vs R	2.346	0.131	0.021	0.886
	T-1 vs T+1	L vs R	0.014	0.905	0.169	0.683
Hemisphere		L vs R	0.768	0.384	0.106	0.746
Stimulus	T vs NTs		28.356	0.000	12.157	0.001
	T-1 vs T+1		7.554	0.008	15.695	0.000

Hemisphere X Stimulus	T vs NTs	L vs R	0.000	0.986	3.383	0.071
	T-1 vs T+1	L vs R	10.506	0.002	0.532	0.469

### 2.2.1.2 Region (anterior-posterior)

Df (1,60) C&FESz	Stimulus	Region	Chronic Sz		FESz	
			F	Sig.	F	Sig.
Group			22.330	0.000	11.500	0.001
Group X Region		A vs P	2.047	0.158	5.108	0.027
Group X Stimulus	T vs NTs		0.873	0.354	12.448	0.001
	T-1 vs T+1		0.775	0.382	0.529	0.470
Grp X Reg X Stim	T vs NTs	A vs P	1.050	0.310	19.612	0.000
	T-1 vs T+1	A vs P	1.239	0.270	1.077	0.303
Region		A vs P	97.062	0.000	100.750	0.000
Stimulus	T vs NTs		16.762	0.000	7.611	0.008
	T-1 vs T+1		4.438	0.039	5.659	0.021
Region X Stim	T vs NTs	A vs P	7.185	0.009	28.445	0.000
	T-1 vs T+1	A vs P	0.040	0.843	0.118	0.732

## 2.2.2 N100 latency

### 2.2.2.1 Hemisphere (left-right)

Df (1,60) CSz, (1,59) FESz	STIMULI	HEM	CSz		FESz	
			F	p	F	p.
Group	1,60		0.824	0.368	4.552	0.037
Group X Hemisphere		L vs R	0.413	0.523	1.275	0.263
Group X Stimulus	T vs NTs		1.289	0.261	1.347	0.250
	T-1 vs T+1		0.376	0.542	0.200	0.657
Group X Hem X Stim	T vs NTs	L vs R	0.819	0.369	1.139	0.290
	T-1 vs T+1	L vs R	0.040	0.843	0.001	0.974
Hemisphere		L vs R	3.752	0.057	0.245	0.622
Stimulus	T vs NTs		4.573	0.037	0.103	0.749
	T-1 vs T+1		4.254	0.044	4.637	0.035
Hemisphere X Stimulus	T vs NTs	L vs R	0.081	0.777	0.592	0.445
	T-1 vs T+1	L vs R	2.329	0.132	1.814	0.183

### 2.2.2.2 Region (anterior-posterior)

Df (1,60) C & FESz	Stimulus	Region	F	Sig.	F	Sig.
Group			0.461	0.500	2.941	0.092
Group X Region		A vs P	2.538	0.116	0.009	0.924
Group X Stimulus	T vs NTs		1.442	0.235	0.143	0.707
	T-1 vs T+1		0.176	0.676	1.544	0.219
Grp X Reg X Stim	T vs NTs	A vs P	0.122	0.728	2.031	0.159
	T-1 vs T+1	A vs P	1.290	0.261	1.107	0.297
Region		A vs P	9.768	0.003	34.976	0.000
Stimulus	T vs NTs		4.921	0.030	4.706	0.034
	T-1 vs T+1		1.012	0.319	1.038	0.312
Region X Stim	T vs NTs	A vs P	11.511	0.001	2.448	0.123
	T-1 vs T+1	A vs P	0.948	0.334	5.777	0.019

### 2.2.3 P200 amplitude

#### 2.2.3.1 Hemisphere (left-right)

Df (1,59)CSz, (1,56) FESz	Contrasts		CSz vs control		FESz vs control	
	Stimulus	Hemisphere	F	p	F	p
Group			9.34	0.003	0.84	0.363
Group X Hemisphere		L vs R	0.00	0.947	0.75	0.390
Group X Stimulus	T vs NTs		1.34	0.251	3.35	0.072
	T-1 vs T+1		1.11	0.297	3.50	0.067
Group X Hem X Stim	T vs NTs	L vs R	0.00	0.971	0.22	0.643
	T-1 vs T+1	L vs R	0.09	0.759	0.05	0.828
Hemisphere		L vs R	0.05	0.818	2.04	0.159
Stimulus	T vs NTs		25.87	0.000	3.13	0.082
	T-1 vs T+1		0.31	0.580	0.91	0.343
Hemisphere X Stimulus	T vs NTs	L vs R	3.16	0.081	0.00	0.949
	T-1 vs T+1	L vs R	10.70	0.002	5.47	0.023

### 2.2.3.2 Region (anterior-posterior)

Df(1,59) C & FESz		Contrast		CSz vs control		FESz vs control	
1,59	Stimulus	Region	F	p	F	p	
Group			8.82	0.004	0.437	0.511	0.167
Group X Region		A vs P	0.01	0.927	3.10		0.083
Group X Stimulus	T vs NT	A vs P	0.30	0.588	3.50		0.066
	T-1 vs T+1	A vs P	0.10	0.755	2.12		0.151
Grp X Region X Stimulus	T vs NT		0.25	0.618	0.38		0.542
	T-1 vs T+1		1.08	0.303	0.60		0.443
Region		A vs P	5.68	0.020	35.49		0.000
Stimulus	T vs NT	A vs P	2.86	0.096	0.05		0.830
	T-1 vs T+1	A vs P	3.47	0.067	0.12		0.735
Region X Stim	T vs NT	A vs P	12.01	0.001	4.62		0.036
	T-1 vs T+1	A vs P	0.21	0.648	0.78		0.380

## 2.2.4 P200 latency

### 2.2.4.1 Hemisphere

Df(1,59)CSz, (1,56) FESz		Contrasts		CSz vs control		FESz vs control	
	Stimulus	Hemisphere	F	Sig.	F	p	
Group			8.701	0.004	554	2.61	0.112
Group X Hemisphere		L vs R	4.67	0.035		0.99	0.325
Group X Stimulus	T vs NT		20.27	0.000		2.79	0.100
	T-1 vs T+1		2.89	0.094		4.65	0.035
Group X Hemisphere X Stimulus	T vs NT	L vs R	0.57	0.454		0.60	0.441
	T-1 vs T+1	L vs R	0.35	0.555		0.32	0.575
Hemisphere		L vs R	0.28	0.599		4.30	0.043
Stimulus	T vs NT		45.89	0.000		10.16	0.002
	T-1 vs T+1		2.01	0.161		29.15	0.000
Hemisphere X Stimulus	T vs NT	L vs R	3.38	0.071		3.86	0.055
	T-1 vs T+1	L vs R	0.03	0.865		0.42	0.518

### 2.2.4.2 Region

Df(1,59) C & FESz	Contrasts	CSz vs control	FESz vs control
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	Stimulus	Region	F	p	F	p
Group			7.77	0.007	3.17	0.080
Group X Region		A vs P	0.82	0.370	1.47	0.230
Group X Stimulus	T vs NTs		17.38	0.000	2.48	0.121
	T-1 vs T+1		2.13	0.150	4.13	0.047
Group X Region X Stimulus	T vs NTs	A vs P	6.49	0.013	3.82	0.055
	T-1 vs T+1	A vs P	1.68	0.201	0.08	0.775
Region		A vs P	10.36	0.002	10.86	0.002
Region X Stimulus	T vs NTs	A vs P	3.41	0.070	4.45	0.039
	T-1 vs T+1	A vs P	0.01	0.904	0.62	0.435
Stimulus	T vs NTs		46.14	0.000	25.21	0.000
	T-1 vs T+1		2.27	0.137	11.45	0.001

## 2.2.5 N200 and P300 components

### 2.2.5.1 Hemisphere (left-right) and region (anterior-posterior)

			Csz vs control			FESz vs control		
	Source	Contrast	df	F	p	df	F	p
N200 amplitude	Hemisphere	L vs R	1,70	0.01	0.906	1,59	4.33	0.042
	Group			0.15	0.700		1.44	0.235
	Hemisphere X Group	L vs R		0.74	0.393		0.10	0.755
	Region	A vs P	1,70	23.44	0.000	1,60	88.80	0.000
	Group			0.05	0.821		0.80	0.314
N200 latency	Region X Group	A vs P		11.59	0.001		4.36	0.041
	Hemisphere	L vs R	1,70	1.69	0.198	1,59	0.00	0.979
	Group			21.89	0.000		5.32	0.025
	Hemisphere X Group	L vs R		0.02	0.895		5.38	0.024
	Region	A vs P	1,70	12.07	0.001	1,60	88.80	0.000
P300 amplitude	Region X Group	A vs P		0.05	0.822		4.36	0.041
	Hemisphere	L vs R	1,70	0.04	0.844	1,63	0.39	0.535
	Group			12.24	0.001		2.5	0.117
	Hemisphere X Group	L vs R		1.31	0.257		0.04	0.843
	Region	A vs P	1,70	153.28	0.000	1,63	160.18	0.000
P300 latency	Region X Group	A vs P		0.45	0.506		4.97	0.029
	Hemisphere	L vs R	1,70	1.76	0.189	1,63	1.47	0.230

Group			0.35	0.553		4.53	0.037
Hemisphere X Group	L vs R		1.22	0.274		3.43	0.069
Region	A vs P	1,70	11.66	0.001	1,63	0.85	0.360
Region X Group	A vs P		3.74	0.057		0.40	0.530

### 3 STUDY 3

#### 3.1 DR

##### 3.1.1 P300 Amplitude

Df(1,26)	Contrasts		FESz vs controls	
	DR	Site	F	p
Group			0.16	0.690
Group X DR	Linear		2.13	0.156
	Quadratic		0.08	0.780
Group X Site		Linear	2.93	0.099
		Quadratic	0.06	0.816
Group X DR X Site	Linear	Linear	0.04	0.838
		Quadratic	1.10	0.304
	Quadratic	Linear	0.50	0.485
		Quadratic	0.47	0.500
DR	Linear		29.40	0.000
	Quadratic		8.05	0.009
DR X Site	Linear	Linear	13.90	0.001
		Quadratic	0.26	0.614
	Quadratic	Linear	0.16	0.692
		Quadratic	0.02	0.889
Site		Linear	82.73	0.000
		Quadratic	20.47	0.000

### 3.1.2 P300 latency

Df(1,26)	Contrasts		FESz vs controls	
	DR	Site	F	Sig.
Group			1.10	0.303
DR	Linear		2.18	0.152
	Quadratic		0.33	0.573
Group X DR	Linear		1.70	0.204
	Quadratic		0.26	0.612
Group X Site		Linear	1.13	0.298
		Quadratic	0.12	0.735
Group X DR X Site	Linear	Linear	2.52	0.125
		Quadratic	5.83	0.023
	Quadratic	Linear	0.20	0.658
		Quadratic	3.63	0.068
DR X Site	Linear	Linear	2.41	0.133
		Quadratic	1.55	0.224
	Quadratic	Linear	11.50	0.002
		Quadratic	0.97	0.333
Site		Linear	0.36	0.555
		Quadratic	0.19	0.666

### 3.1.3 RT

Df(1,26)	Contrasts	F	p
Group		0.21	0.061
DR	Linear	0.36	0.552
	Quadratic	0.19	0.664
DR X Group	Linear	0.14	0.708
	Quadratic	0.59	0.448

## 3.2 DA

### 3.2.1 P300 amplitude

Df(1,26)	Contrasts		FESz vs controls	
	DR	Site	F	Sig.
Group			0.26	0.613
DA	Linear		0.01	0.917
	Quadratic		0.00	0.958
Group X DA	Linear		1.82	0.189
	Quadratic		0.29	0.597
Group X Site		Linear	1.63	0.213
		Quadratic	1.42	0.245

Group X DA X Site	Linear	Linear	0.03	0.859
		Quadratic	0.02	0.888
	Quadratic	Linear	0.13	0.726
		Quadratic	1.14	0.296
DA X Site	Linear	Linear	0.32	0.574
		Quadratic	0.02	0.884
	Quadratic	Linear	0.01	0.905
		Quadratic	0.48	0.493
Site		Linear	38.60	0.000
		Quadratic	17.22	0.000

### 3.2.2 P300 Latency

Df(1,26)	Contrasts		FESz vs control	
	DA	Site	F	p
Group			0.12	0.732
DA	Linear		1.00	0.326
	Quadratic		0.30	0.591
Group X DA	Linear		2.41	0.133
	Quadratic		3.91	0.059
Group X Site		Linear	0.19	0.669
		Quadratic	1.31	0.262
Group X DA X Site	Linear	Linear	0.30	0.591
		Quadratic	0.14	0.715
	Quadratic	Linear	10.28	0.004
		Quadratic	0.03	0.870
DA X Site	Linear	Linear	6.67	0.016
		Quadratic	0.01	0.915
	Quadratic	Linear	0.46	0.504
		Quadratic	0.14	0.711
Site		Linear	0.51	0.480
		Quadratic	2.96	0.097

### 3.2.3 RT



Df(1,26)	Contrasts	FESz vs control	
		F	<i>p</i>
GROUP		1.83	0.188
DA	Linear	8.89	0.006
	Quadratic	7.59	0.011
Group X DA	Linear	0.04	0.848
	Quadratic	0.53	0.472

### 3.3 Continuing (NN, TT) and discontinuing (TN, NT) series.

#### 3.3.1 P300 amplitude

Df(1,26)	Contrasts			FESz vs Controls	
	Sequence	Stimulus	Site	F	<i>p</i>
Group				3.06	0.092
Sequence	cont vs discount			1.21	0.282
Stimulus		T vs N		0.07	0.793
Group X Sequence	cont vs discount			0.00	0.983
Group X Stimulus		T vs N		3.83	0.061
Group X Site			Linear	0.06	0.808
			Quadratic	0.07	0.788
Group X Sequence X Stimulus	cont vs discount	T vs N		0.17	0.686
Group X Sequence X Site	cont vs discount		Linear	1.22	0.280
			Quadratic	2.37	0.136
Group X Stimulus X Site		T vs N	Linear	2.13	0.157
			Quadratic	0.11	0.742
Group X Sequence X Stimulus X Site	cont vs discount	T vs N	Linear	0.26	0.615
			Quadratic	4.12	0.053
Sequence X Stimuli	cont vs discount	T vs N		3.63	0.068
Sequence X Site	cont vs discount		Linear	0.57	0.456
			Quadratic	0.00	0.980
Sequence X Stimulus X Site	cont vs discount	T vs N	Linear	1.12	0.300
			Quadratic	3.47	0.074

Stimulus X Site	T vs N	Linear	4.54	0.043
		Quadratic	0.47	0.498
Site		Linear	47.41	0.000
		Quadratic	0.01	0.916

### 3.3.2 N100 amplitude

Df (1,26)	Contrasts			FESz vs Controls	
	SEQ	STIM	SITE	F	Sig.
Group				3.06	0.092
Sequence	cont vs discount			1.21	0.282
Stimulus		T vs N		0.07	0.793
Group X Sequence	cont vs discount			0.00	0.983
Group X Stimulus		T vs N		3.83	0.061
Group X Site			Linear	0.06	0.808
			Quadratic	0.07	0.788
Group X Sequence X Stimulus	cont vs discount	T vs N		0.17	0.686
Group X Sequence X Site	cont vs discount		Linear	1.22	0.280
			Quadratic	2.37	0.136
Group X Stimulus X Site		T vs N	Linear	2.13	0.157
			Quadratic	0.11	0.742
Group X Sequence X Stimulus X Site	cont vs discount	T vs N	Linear	0.26	0.615
			Quadratic	4.12	0.053
Sequence X Stimuli	cont vs discount	T vs N		3.63	0.068
Sequence X Site	cont vs discount		Linear	0.57	0.456
			Quadratic	0.00	0.980
Sequence X Stimulus X Site	cont vs discount	T vs N	Linear	1.12	0.300
			Quadratic	3.47	0.074
Stimulus X Site		T vs N	Linear	4.54	0.043
			Quadratic	0.47	0.498
Site			Linear	47.41	0.000

	Quadratic	0.01	0.916
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## 4 STUDY 4

### 4.1.1 N100 amplitude

	Stimulus	Site	FESz vs ADHD+NC <i>df</i> (1,58)		ADHD vs NC <i>df</i> (1,38)	
			<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Group			5.91	0.02	0.30	0.589
Grp X Stim	T vs NTs		9.96	0.003	0.27	0.605
	T-1 vs T+1		1.79	0.187	0.77	0.385
Grp X Site		Cz vs Fz & Pz	4.33	0.042	0.86	0.360
		Fz vs Pz	1.89	0.174	0.35	0.558
Grp X Stim X Site	T vs NTs	Cz vs Fz & Pz	0.16	0.691	0.12	0.729
		Fz vs Pz	18.47	0.000	3.85	0.057
	T-1 vs T+1	Cz vs Fz & Pz	0.01	0.904	0.87	0.357
		Fz vs Pz	3.46	0.068	0.51	0.480
Stimulus	T vs NTs		5.31	0.025	19.76	0.000
	T-1 vs T+1		13.07	0.001	16.19	0.000
Stimulus X Site	T vs NTs	Cz vs Fz & Pz	3.58	0.064	3.20	0.082

		Fz vs Pz	3.46	0.068	51.22	0.000
	T-1 vs T+1	Cz vs Fz & Pz	0.01	0.904	4.76	0.035
		Fz vs Pz	3.46	0.068	9.80	0.003
Site		Cz vs Fz & Pz	5.88	0.018	10.85	0.002
		Fz vs Pz	45.77	0.000	44.90	0.000

### 4.1.2 N100 Latency

			FESz vs ADHD+NC <i>df</i> (1,58)		ADHD vs NC <i>df</i> (1,38)	
Group	Stimulus	Site				
			0.06	0.81	0.48	0.49
Grp X Stim	T vs NTs		5.63	0.0210	0.01	0.9247
	T-1 vs T+1		2.71	0.1050	0.08	0.7768
Grp X Site		Cz vs Fz & Pz	0.06	0.8074	2.92	0.0957
		Fz vs Pz	0.30	0.5839	1.50	0.2289
Grp X Stim X Site	T vs NTs	Cz vs Fz & Pz	1.92	0.1708	0.69	0.4125
		Fz vs Pz	3.28	0.0754	0.19	0.6653
	T-1 vs T+1	Cz vs Fz & Pz	0.47	0.4965	0.13	0.7202
		Fz vs Pz	3.65	0.0611	0.12	0.7264
Stimulus	T vs NTs		1.04	0.3120	1.85	0.1822
	T-1 vs T+1		0.06	0.8073	2.28	0.1393

Stimulus X Site	T vs NTs	Cz vs Fz & Pz	0.03	0.8631	1.14	0.2932
		Fz vs Pz	0.14	0.7121	4.41	0.0425
	T-1 vs T+1	Cz vs Fz & Pz	6.02	0.017	0.81	0.3752
		Fz vs Pz	4.54	0.037	0.02	0.8989
Site		Cz vs Fz & Pz	2.74	0.1032	1.96	0.1694
		Fz vs Pz	55.49	0.0000	50.40	0.0000

### 4.1.3 P200 amplitude

	Stimulus	Site	FESz vs ADHD+NC <i>df</i> (1,58)		ADHD vs NC <i>df</i> (1,38)	
Group			0.18	0.67	0.00	0.99
Grp X Stim	T vs NTs		11.18	0.0015	0.20	0.657
	T-1 vs T+1		5.71	0.0201	1.37	0.249
Grp X Site		Cz vs Fz & Pz	5.57	0.0216	0.95	0.3353
		Fz vs Pz	3.34	0.0728	3.00	0.0912
Grp X Stim X Site	T vs NTs	Cz vs Fz & Pz	0.06	0.8050	0.65	0.4239
		Fz vs Pz	4.30	0.0426	0.12	0.7274
	T-1 vs T+1	Cz vs Fz & Pz	0.20	0.6535	0.04	0.8457
		Fz vs Pz	0.57	0.4549	0.03	0.8529
Stimulus	T vs NTs		1.58	0.2144	14.44	0.0005
	T-1 vs T+1		2.97	0.0904	14.23	0.0006

Stimulus X Site	T vs NTs	Cz vs Fz & Pz	5.96	0.0177	2.80	0.1022
		Fz vs Pz	11.08	0.0015	27.05	0.0000
	T-1 vs T+1	Cz vs Fz & Pz	3.98	0.0508	1.83	0.1837
		Fz vs Pz	2.32	0.1335	4.62	0.0381
Site		Cz vs Fz & Pz	45.71	0.0000	51.64	0.0000
		Fz vs Pz	24.36	0.0000	26.62	0.0000

#### 4.1.4 P200 Latency

			FESz vs ADHD+NC <i>df</i> (1,58)		ADHD vs NC <i>df</i> (1,38)	
Group		Site	0.29	0.59	0.97	0.330
Grp X Stim	T vs NTs		0.78	0.3820	1.45	0.236
	T-1 vs T+1		16.13	0.0002	0.00	0.9711
Grp X Site		Cz vs Fz & Pz	0.37	0.5444	0.24624	0.622593
		Fz vs Pz	1.04	0.3122	0.087545	0.768933
Grp X Stim X Site	T vs NTs	Cz vs Fz & Pz	3.72	0.0586	0.76	0.387
		Fz vs Pz	1.45	0.2337	1.84	0.182
	T-1 vs T+1	Cz vs Fz & Pz	0.55	0.4627	0.55	0.465
		Fz vs Pz	11.32	0.0014	1.62	0.211
Stimulus	T vs NTs		53.17	0.0000	33.70	0.000
	T-1 vs T+1		1.93	0.1697	5.20	0.028
Stimulus X Site	T vs NTs	Cz vs Fz & Pz	0.21	0.6483	3.78	0.059

	T-1 vs T+1	Fz vs Pz	3.37	0.0716	6.68	0.014
		Cz vs Fz & Pz	0.52	0.4728	0.00	0.987
		Fz vs Pz	1.94	0.1685	4.52	0.040
	Site	Cz vs Fz & Pz	0.48	0.4897	0.01	0.939
		Fz vs Pz	9.61	0.0030	3.89	0.056

#### 4.1.5 N200 amplitude

	Site	FESz vs ADHD+NC <i>df</i> (1,58)		ADHD vs NC <i>df</i> (1,38)	
		<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Group		2.79	0.10	0.15	0.6982
Group X Site	Cz vs Fz & Pz	0.01	0.9340	0.35	0.5560
	Fz vs Pz	6.94	0.0108	0.28	0.6029
Site	Cz vs Fz & Pz	7.95	0.0066	4.97	0.0318
	Fz vs Pz	93.34	0.0000	99.64	0.0000

#### 4.1.6 N200 latency

	Site	FESz vs ADHD+NC <i>df</i> (1,58)		ADHD vs NC <i>df</i> (1,38)	
		<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Group		0.69	0.41	0.50	0.48
Group X Site	Cz vs Fz & Pz	1.21	0.2763	0.01	0.9390
	Fz vs Pz	0.00	0.9818	1.12	0.2966
Site	Cz vs Fz & Pz	4.36	0.0412	9.58	0.0037

Fz vs Pz	24.91	0.0000	23.13	0.0000
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#### 4.1.7 P300 amplitude

N2amp	Site	FESz vs ADHD+NC		ADHD vs NC	
		<i>df</i> (1,58)		<i>df</i> (1,38)	
		<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Group		0.00	0.99	7.88	0.0078
Group X Site	Cz vs Fz & Pz	0.10	0.7486	1.07	0.3082
	Fz vs Pz	6.23	0.0154	0.57	0.4532
Site	Cz vs Fz & Pz	2.23	0.1406	0.98	0.3293
	Fz vs Pz	138.53	0.0000	145.57	0.0000

#### 4.1.8 P300 latency

N2amp	Site	FESz vs ADHD+NC		ADHD vs NC	
		<i>df</i> (1,58)		<i>df</i> (1,38)	
		<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Group		0.53	0.4728	0.71	0.4043
Group X Site	Cz vs Fz & Pz	0.10	0.7575	0.17	0.6815
	Fz vs Pz	0.49	0.4895	0.00	0.9514
Site	Cz vs Fz & Pz	1.98	0.1671	1.94	0.1692
	Fz vs Pz	0.08	0.7855	0.12	0.7332