Offprint from
Journal of Psychophysiology 11 (1997) 173–187

The use of Gaussian component modelling to elucidate average ERP component overlap in schizophrenia

Albert R. Haig[1], Christopher Rennie[2], Evian Gordon[1, 3]

[1] University of Sydney, Australia, [2] Department of Psychiatry, Westmead Hospital, Westmead, Australia,
[3] Cognitive Neuroscience Unit, Westmead Hospital, Sydney, Australia.

Accepted for publication: November 4, 1996

Keywords: ERP, schizophrenia, modelling, component, Gaussian, simulated annealing

Abstract Abnormalities of auditory oddball late ERP components have been reported in schizophrenia in a variety of studies. The possibility that component overlap may be contaminating traditional peak-to-baseline amplitude estimates has been previously recognized. Resolving the effects of component overlap requires the adoption of model assumptions about the component structure of the ERP. There are substantial difficulties relating to the assumptions involved with conventional methods of resolving component overlap, such as principal component analysis (PCA) and related techniques. In this study we modelled target auditory oddball average ERP data from 25 unmedicated and 25 medicated schizophrenics and 25 normal controls. Four Gaussian functions were employed (one for each of the four main components N1, P2, N2, and P3), each having three parameters (amplitude, latency, and width). By using the method of simulated annealing, we obtained the best possible fit between the four-Gaussian model waveforms and the actual average ERPs, within certain constraints imposed *a priori* on the basis of knowledge about the ERP components in question. There was a good fit between the modelled and measured ERP data. The four Gaussian method avoids the most difficult assumptions of PCA and related methods, although it involves alternative model assumptions. Component overlap was shown to be potentially relevant in relation to amplitude estimates for all four components, especially P2 and P3, but also N2 and to a lesser extent N1. Furthermore, the three groups of subjects each appeared to be affected by overlap in different ways, as different clinical findings were observed for both N1 and P3 dependent upon whether traditional peak-to-baseline or Gaussian amplitude estimates were employed. Exploring component overlap in schizophrenia by means of techniques with alternative model assumptions may help to clarify the ERP abnormalities in this disorder.

Introduction

The traditional auditory oddball late-component ERP waveform consists of four primary components, N1, P2, N2, and P3, each of which may in turn consist of multiple sub-components. Each of these components is a deflection of relatively short duration from ERP baseline. Abnormalities of N1 and P3 in particular have been reported in schizophrenia in a variety of studies (Pritchard, 1986). It has been claimed that a decreased P3 amplitude in schizophrenia is one of the most reliable biological findings in this disorder (Ford, White, Lim, & Pfefferbaum, 1994).

The peaks of these four ERP components (N1, P2, N2, P3) are typically identified in the average response. In this study we employ a simple model of the stimulus-related response based on four components of varying amplitude, latency, and width. This involves an understanding of a component as being not just a peak in the waveform, but a whole deflection (positive or negative) with a particular shape which is added in to the rest of the signal. Under this assumption, it is possible to conceive of an alternative to the usual peak-to-baseline measure of amplitude, namely the component amplitude *in isolation from other components.* Furthermore, if the model turns out to be justified, then this would be a better measure of amplitude, as it would not be affected by component overlap.

The possibility of component overlap is an

important concern when making amplitude estimates. The peak-to-baseline measure will not be an accurate index of the actual component amplitude if there is significant overlap between two components, since overlap will offset the component being examined from the baseline. For example, if two large components of opposite polarity overlap to a great extent (their peak latency is almost the same) the resultant peaks in the waveform will be very small, and thus the actual component amplitude will be obscured. If we wish to examine the time-locked functional processes which relate to each ERP component, it is imperative that accurate component amplitude estimates be employed. The method described in this paper provides one approach to achieve this goal.

One class of techniques has been advocated as a means of resolving the problem of component analysis. This class includes principal component analysis (PCA) and varimax rotation, factor analysis, and related methods (Chatfield & Collins, 1980a; Donchin, Tueting, Ritter, Kutas, & Heffley, 1975; Hunt, 1985; McGillem & Aunon, 1987; Rogers, 1991). All of these techniques involve analyzing a given set of ERP signals together as a group (these signals may be single trials or averages, and may be obtained from a single electrode site or from multiple sites), and deriving from these signal vectors a small set of vectors or factors which account for all or most of the structure of the signal vectors and which are claimed to represent the underlying components. However, there are some theoretical doubts about the adequacy of these techniques (for example, see Rogers, 1991). Most of them do not take into account the possibility of latency differences in the ERP components between the signals under consideration (Möcks, 1986). In most circumstances, this is a serious problem. None of them take into account possible differences in the shape of components, and most importantly, the width of components between signals. That is, the temporal evolution of a given component may well be such that it varies in its total duration from trial-to-trial or across sites. Often, Gaussian distributions are assumed for the variables. Frequently, orthogonality of components is assumed, a most implausible assumption, and independence of components is always assumed. However, it seems quite likely that distinct physiological components may have statistical relationships between them, making an assumption of independence difficult to sustain. The result of all these problems is that the "components" derived from these techniques may represent complex mathematical combinations of the real physiological ERP components, resulting in difficulties in interpretation and comparisons across subjects.

In the case of PCA and varimax rotation, empirical studies with simulated data have demonstrated that these problems are not only theoretical (Möcks & Verleger, 1986; Rogers, 1991; Wood & McCarthy, 1984). However, there is a two-fold problem here. The first, in relation to studies of simulated data, is that simulated data is only valuable insofar as it resembles the real data, and this in turn presupposes that the structure of the real data is understood, because otherwise this resemblance is very difficult to establish. Secondly, in empirical studies using real ERP data, there is simply no "gold standard" to which results can be compared to establish their veracity. This is not such a problem in itself, so long as it is kept in mind that no measures derived from any current technique can lay claim to physiological reality except insofar as these measures are useful correlates of psychological, physiological, and clinical variables.

Any approach to the problem of component overlap must involve model assumptions because of the indeterminacy of the problem. The method introduced in this paper makes alternative assumptions to the previous methods, which in some respects at least may be more plausible. This model does not in any way assume independence of components, and treats each signal under consideration in isolation from all the rest, therefore avoiding any assumptions about amplitude, latency, or width variability between signals. It does, however, assume that there are only four primary components (negative, positive, negative, and positive in that order) with shape approximately Gaussian, this being the crucial assumption. Unfortunately, there is insufficient detailed physiological knowledge of the generation of the ERP components and in particular the temporal evolution of each component at the generator site or sites for such a model to be based on *a priori* physiological grounds. In single trial ERP analysis, a number of different models of component shape have been em-

ployed, such as a half-cycle 2 Hz sine wave (Ford et al., 1994), a fading oscillation (O'Connor, Simon, & Tasman, 1984) and an ex-Gauss function (Verleger & Wascher, 1995). We have chosen to model each component as a Gaussian deflection, because this represents a simple compromise starting point in relation to the issue of component overlap. We have not attempted to model subcomponents of the four main components, although there is some evidence that P3 in particular may consist of multiple subcomponents, most notably the well-known subcomponents P3a and P3b. The more components one attempts to model, the more parameters must be introduced and the more complex the model becomes. The subcomponents are much more difficult to differentiate than the four main components, and a four-Gaussian model may provide a sufficient approximation, although this must be taken into account in interpretation of the results.

The aim of this study is to examine this Gaussian component model in relation to the N1, P2, N2, and P3 ERP component findings in schizophrenia, using average ERP data where we can also reliably identify the component peaks by means of manual observation. The results of this study cannot constitute a proof that the underlying components are actually Gaussian, but, if successful, would lend a degree of plausibility to the model and would provide one alternative avenue for elucidating component overlap.

Having adopted the four-Gaussian model, we have a minimization problem involving 12 parameters. There are four Gaussian components, each with three parameters (amplitude, latency, and width). We wish to obtain the values of these parameters which result in the best fit between the theoretical model waveform and actual ERP data, in a least squares sense (with appropriate constraints to ensure that the Gaussian components do not end up modelling irrelevant features of the waveform). The minimization routines which are generally employed in this context are inadequate because they lack globally optimal properties. Most minimization algorithms, including such techniques as conjugate gradient and variable metric methods (Press, Flannery, Teukolsky, & Vetterling, 1992), arrive at a solution which represents a nearby local minimum in the energy function. In this study we employ a technique known as simulated annealing (Kirkpatrick, Gelatt, & Vecchi, 1983; Metropolis, Rosenbluth, Rosenbluth, Teller, & Teller, 1953), also known as the "Metropolis algorithm," which will obtain the global minimum, or absolute best fit, between the model waveforms and the real ERPs. In the case of modelling the ERP average, a globally optimal solution may be readily obtained because the noise has been reduced considerably by the averaging process and the resultant energy surface is therefore relatively smooth, with hopefully a well-defined minimum. If successful, however, the model could be extended to single trial analysis, in which case it would be expected that a globally optimal minimisation algorithm would become much more important, as the background ongoing EEG is likely to result in a very "rough" energy surface with many poor local minima in which algorithms lacking globally optimal properties may be trapped. We have employed simulated annealing in a previous ERP study (Haig, Gordon, Rogers, & Anderson, 1995), although in a completely different context to this study, in relation to cluster analysis of single trial ERPs in order to determine possible subtypes of response. Gerson, Cardenas, and Fein (1994) have also employed simulated annealing in relation to ERPs, again in a quite different context (equivalent dipole source localization).

In order to ensure that the Gaussian components do not model features of the waveform which are clearly unrelated to the four components of interest, it is necessary to introduce constraints to the minimization problem. This can be thought of as restricting the optimization to a certain bounded region of the solution space, which is known on *a priori* grounds to contain the result. In the case of the four ERP components, there are constraints in terms of the latency window in which they are known to occur (see methods for details), their order and the sign of their amplitude (must be negative, positive, negative, positive in that order for N1, P2, N2, and P3), how close together they may be, and their width. These constraints may be imposed on the minimization procedure so that it determines the globally optimal solution *within the bounds of the constraints.*

In this study we applied this method to target auditory oddball data from unmedicated and medicated schizophrenic patients and age

and sex matched normal controls, in order to determine the role component overlap might be playing in relation to the traditional peak-to-baseline amplitude findings.

Methods and materials

Subjects

Data from 75 subjects was examined in this study, consisting of 25 unmedicated schizophrenics, 25 medicated schizophrenics, and 25 normal controls. In each of the three groups, subjects were sex-matched and age-matched to within 5 years (17 males and 8 females in each group). Unmedicated schizophrenic males had mean age 23.8 years (SD = 6.4) and unmedicated females 30.4 years (SD = 7.9). Medicated schizophrenic males had mean age 25.9 years (SD = 6.1) and medicated females 29.1 years (SD = 7.7). Normal males had mean age 25.2 years (SD = 7.5) and normal females 30.5 years (SD = 7.2).

Schizophrenic patients were obtained from the inpatient and outpatient populations of two major teaching hospitals of the University of Sydney. Patients were administered the Composite International Diagnostic Interview (CIDI) (Robins, Wing, & Healer, 1987) and satisfied both DSM III-R criteria (American Psychiatric Association, 1987) and Research Diagnostic Criteria (Endicott & Spitzer, 1979) for schizophrenia. Unmedicated patients had not received oral psychotropic medication for at least 6 weeks or depot antipsychotics for 3 months prior to testing. Patients had no history of significant head injury, ECT, epilepsy, developmental disability, or other major neurological or psychiatric disturbance. Normal subjects were volunteers recruited from non-departmental hospital staff and the surrounding community, who disavowed any psychiatric history, neurological disorder, or substance abuse. Written consent was obtained from all subjects prior to testing in accordance with National Health and Medical Research Council guidelines.

SANS and SAPS scores (Andreasen & Olsen, 1982) were obtained for the schizophrenic patients. The mean SANS score in unmedicated schizophrenics was 12.3 (SD = 4.6) and the mean SAPS score in unmedicated patients was 9.7 (SD = 4.5). The mean SANS score in the medicated patients was 10.0 (SD = 6.0) and the mean SAPS score was 6.8 (SD = 4.5). Thus, as expected, the unmedicated patients had worse negative and positive symptom profiles than the medicated patients.

Procedure

Subjects were seated in a sound and light attenuated room. An electrode cap (Blom & Anneveldt, 1982) was used to acquire data from Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, Pz, P3, P4, O1, and O2 scalp sites. Linked earlobes served as the reference. Electrodes placed 1 cm above the outer canthus of the left eye and below the outer canthus of the right eye served as the EOG bipolar recording. EOG contaminated epochs (exceeding ± 100 μV) were automatically rejected. Skin resistance at each site was < 5 kOhms. The ERP data was collected according to a standard auditory "oddball" paradigm (Anderson, Rennie, Gordon, Howson, & Meares, 1991). Stereo headphones conveyed regular tones of 1000 Hz at an interval of 1.3 seconds to both ears. The subjects were instructed to ignore these tones (task irrelevant). A second target (task relevant) tone of 1500 Hz was presented, randomly intermixed with the lower tone, the only constraint being that two high tones were never presented in succession. Of the tones, 85% were task irrelevant and 15% were targets. The subjects were instructed to respond to the target tones by pressing two reaction-time buttons, as fast and accurately as possible, with the middle finger of each hand (to counterbalance motor effects). All tones were presented at 60 dB above the subject's auditory threshold (determined prior to recording). Only correctly identified target epochs for which a button press response was obtained within 1 s of the target tone were analyzed. The recording session was continued until 30 correctly identified target epochs uncontaminated by eye movements were acquired. Each subject had their eyes open and was instructed to fixate on a colored dot in the center of a screen, in order to minimize eye movements. The sampling rate was 256 Hz, and the duration of each epoch analyzed was 1 s, from 300 ms pre-stimulus to 700 ms post-stimulus. A 70 Hz low-pass filter was applied to the signals prior to digitization.

In order to reduce the dimensionality of the data from 256 samples per epoch to only 64,

the following procedure was employed. First, a digital filter was applied to each single trial with the half-amplitude (–6 dB) point at 30 Hz, a passband of 0–25 Hz, and a stopband of 35 Hz and above, using a 28.6% cosine taper (Tukey) filter function (applied in the frequency domain). Each single trial was then subsampled at a rate of 128 Hz. This reduced the dimensionality from 256 to 128 and prevented aliasing in the process (since the highest frequency component of 35 Hz was well below the Nyquist frequency of 64 Hz). Then only the portion of the signal from 0 to 500 ms post-stimulus was retained and the rest (–300 to 0 ms and 500 to 700 ms) was discarded. This reduced the dimensionality down to 64 samples. This dimensionality reduction made the analysis more computationally tractable, without losing any relevant component structure. The resulting 30 single trial epochs from each site in each subject were then averaged. Finally, for each average ERP waveform the pre-stimulus baseline average was computed (–300 to 0 ms). This pre-stimulus baseline value was then subtracted from every sample in the average ERP waveform. This was done to center the average waveform around zero, relative to the pre-stimulus baseline average.

Analysis

The four Gaussian component model and error measure

The real ERP average from a particular site in one subject was modelled by obtaining the absolute best fit in a least squares sense (given certain constraints which are detailed later) with a four-Gaussian component curve. Each of the four Gaussian components had three parameters, A (amplitude), B (latency), and C (width), and the following form:

$$y = Ae^{-\left(\frac{x-B}{C}\right)^2} \quad (1)$$

The modelled curve was computed as the sum of the four Gaussian curves. If the 12 parameters of the model curve are denoted $A_1, B_1, C_1, A_2, B_2, C_2, A_3, B_3, C_3, A_4, B_4$, and C_4, it therefore has the form:

$$y = A_1 e^{-\left(\frac{x-B_1}{C_1}\right)^2} + A_2 e^{-\left(\frac{x-B_2}{C_2}\right)^2} + A_3 e^{-\left(\frac{x-B_3}{C_3}\right)^2} + A_4 e^{-\left(\frac{x-B_4}{C_4}\right)^2} \quad (2)$$

The model curve was computed at 64 samples in time over the period 0 to 500 ms, exactly as for the real data.

For a given average ERP curve, denoted as a vector **x** whose elements $x_1, x_2, x_3, \ldots x_{64}$ are the 64 samples in time, and a given four Gaussian component model curve, denoted as a vector **y** whose elements $y_1, y_2, y_3, \ldots y_{64}$ are the 64 computed model values in time, the total squared error or distortion is given by:

$$d(\mathbf{x},\mathbf{y}) = \|\mathbf{x}-\mathbf{y}\|^2 = \sum_{i=1}^{64} (x_i - y_i)^2 \quad (3)$$

The purpose of the simulated annealing procedure was, for a given real average ERP waveform, to determine the values of the 12 parameters $A_1 \ldots C_4$ within the constraints which gave the smallest possible value of this squared error. That is, the global minimum of the energy function in the allowable constrained region was determined. This is the absolute best match between real and model data in a least squares sense.

Full details of the simulated annealing procedure and the imposed constraints may be found in the appendix.

Manual identification of components

We compared the latency and amplitude values from the Gaussian functions with the latency and amplitude of the manually identified N1, P2, N2, and P3 components scored using a cursor by a trained observer (Anderson et al., 1991). This manual identification procedure was undertaken without knowledge of the results of the four Gaussian model procedure, to avoid possible subjective bias in the identification of components.

The component latencies were computed by the four Gaussian component method, and compared to those determined by a trained observer. Estimates by the former method were classified as "correct" if the differences were less than or equal to 25 ms, otherwise they were classified as "incorrect."

Evaluation of model waveform in relation to the average

The next step in relation to the average involved determining if the model waveforms closely reflected the real structure of the average in relation to the components. In order to

do this, the following procedure was adopted. At the latency of the components as identified manually (that is, at four different latencies altogether), the sample value in the model waveform was subtracted from the sample value in the real average ERP. These difference values were analyzed for each component latency to determine if they differed significantly from the expected value of zero if the waveforms had exactly the same structure at these points. Each subject had 15 difference values (from the 15 recording sites), and each group of 25 subjects was analyzed individually to determine if the means across sites differed significantly from the expected value of zero at every site. This was done by means of MANOVA, using a one-sample Hotelling's T^2-test (Chatfield & Collins, 1980 b).

Between group and between measure comparisons

The estimate of component amplitude from the four Gaussian method of interest was the value of the parameter A (equations 1 and 2) for each component, that is, the component amplitude from the base of the Gaussian to its peak. This is a "pure" estimate of component amplitude, uncontaminated by component overlap. By way of comparison, the component amplitude in the real average ERP waveform at the latency identified manually by the trained observer was also computed. This was a peak-to-baseline amplitude, which since the baseline was zero (pre-stimulus baseline average had been subtracted from the waveform), was simply the peak sample value.

Between group topographical statistical analysis was then performed using MANOVA (Hotelling's T^2-test) for each of these two measures. Three comparisons were performed for each measure: normals versus unmedicated schizophrenics; normals versus medicated schizophrenics; and unmedicated versus medicated schizophrenics. In addition, in each group the two measures themselves were compared. The 15 electrode site values from each of the 25 subjects in one group were compared with the 15 electrode site values from the 25 subjects in the other group using a two-sample Hotelling's T^2-test (Chatfield & Collins, 1980 b), a form of MANOVA, to determine if the means across sites differed significantly between the two groups. In addition to this analysis, for each measure the value averaged across sites and subjects for each group is reported, and for significant differences, the number of sites at which the measure was increased and/or decreased in one group compared to the other. In the P3 amplitude between group comparisons, in addition to Hotelling's T^2-test, a single global mean value (the mean of the values from all 15 electrode sites) was derived for each subject, and the 25 global mean values from one group were compared to the 25 global mean values from the other, using a Student's t-test. This enabled the specific hypothesis of an overall decrease (or increase) in P3 amplitude in one group compared to the other to be tested.

Results

Figure 1 shows the real average ERP from 10 different selected normal subjects at electrode site Cz, superimposed on the corresponding four Gaussian component model waveforms in each case. This gives a visual impression of the morphological similarities between the real ERP and model waveforms within individuals.

Figure 2 shows the grand average in the normals (across all 25 subjects) at site Cz of each of the four Gaussian components in isolation, together with superimposed grand averages of the four Gaussian component model waveforms and real average ERPs at this site. Figure 3 shows the same for the unmedicated schizophrenics, and Figure 4 for the medicated schizophrenics, all with the same scale. This gives a visual impression of the average morphologies of the four components in isolation and also as a complete waveform in each of the three groups at site Cz.

Comparisons of latency

In the normals, across all 15 sites, the Gaussian component latency was "correct" (within 25 ms of the manually identified latency) in 84.2% of cases for N1, 65.5% of cases for P2, 63.3% of cases for N2, and 76.4% of cases for P3. These components were missing (as judged by manual inspection) in 0.5% of cases for N1, 11.1% of cases for P2, 9.5% of cases for N2, and 0.0% of cases for P3, in all of which cases the Gaussian latency was judged to be "incorrect."

Across all 15 sites in the unmedicated

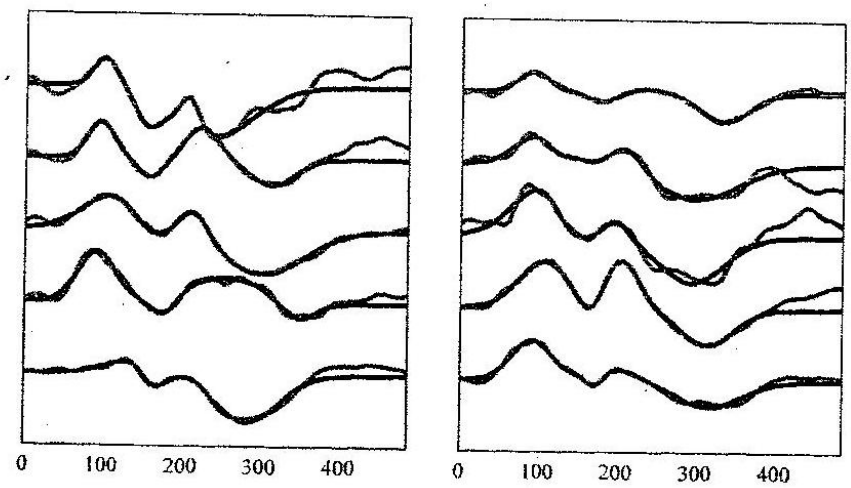

Figure 1 The average ERP waveforms from 10 selected normal subjects at the Cz electrode site (gray lines), with superimposed four Gaussian model waveforms (black lines). In each case the model waveform is a close fit to the real ERP, especially in relation to the N1, P2, N2, and P3 components. Note that frequently in the ERPs there is a post-P3 negativity, which is not taken into account by the model. The time scale is from 0 to 500 ms.

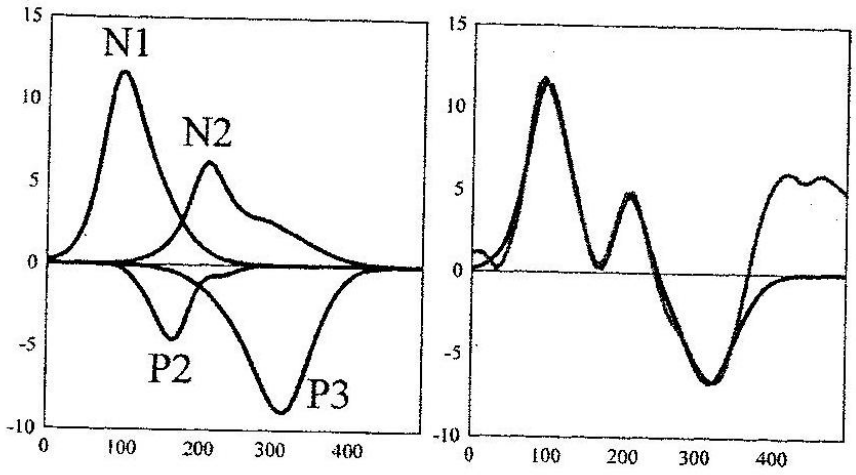

Figure 2 This shows the grand averages of the Gaussian components in isolation (on the left), and the real average ERP and complete four-Gaussian model waveforms (superimposed on the right), for the 25 normal subjects at site Cz. The *x*-axis units are ms, and the *y*-axis units are (sign reversed) μV. This illustrates how the Gaussian components combine to form the overall model waveform. Note the presence of the post-P3 negativity not accounted for by the model.

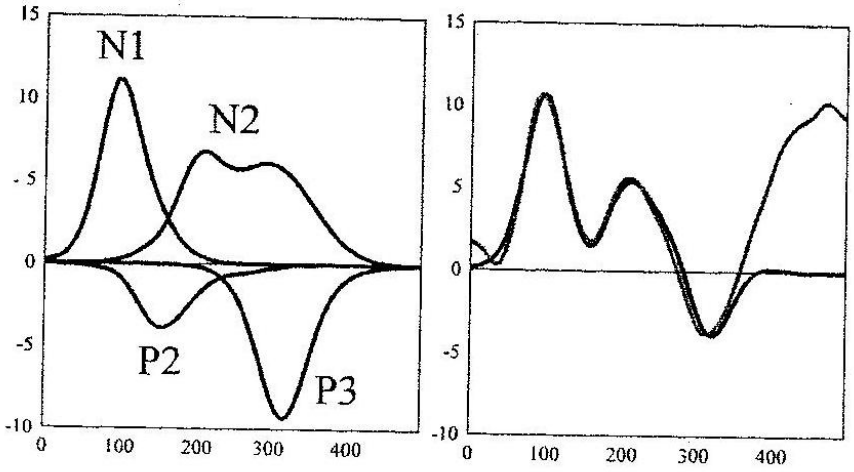

Figure 3 This shows the grand averages of the Gaussian components in isolation (on the left), and the real average ERP and complete four-Gaussian model waveforms (superimposed on the right), for the 25 unmedicated schizophrenics at site Cz. The *x*-axis units are ms, and the *y*-axis units are (sign reversed) μV.

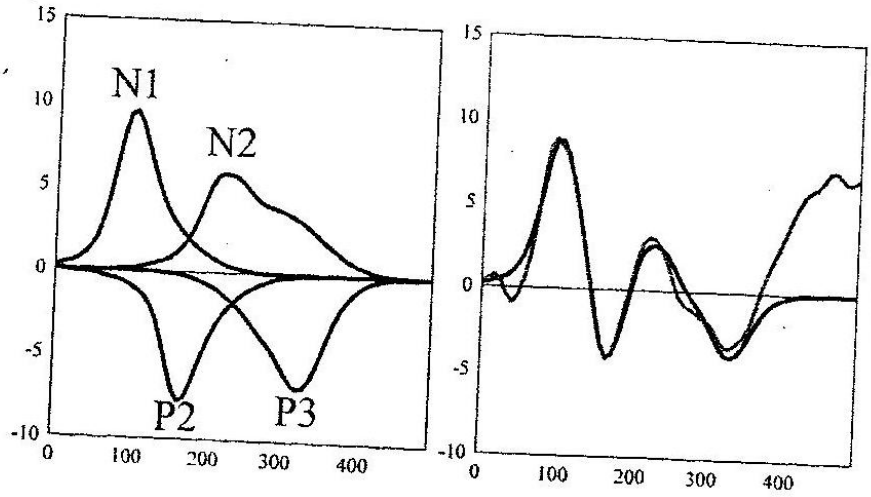

Figure 4 This shows the grand averages of the Gaussian components in isolation (on the left), and the real average ERP and complete four-Gaussian model waveforms (superimposed on the right), for the 25 medicated schizophrenics at site Cz. The *x*-axis units are ms, and the *y*-axis units are (sign reversed) μV.

schizophrenics, the Gaussian latency was "correct" compared to manual identification in 79.2% of cases for N1, 66.6% of cases for P2, 55.6% of cases for N2, and 76.4% of cases for P3. N1 was absent on manual inspection in 1.4% of cases, P2 in 11.2% of cases, N2 in 10.4% of cases, and P3 in 0.8% of cases.

Across all sites in the medicated schizophrenics, the Gaussian latency was "correct" in 82.9% of cases for N1, 71.2% of cases for P2, 62.8% of cases for N2, and 73.4% of cases for P3. The components were missing on manual inspection in 1.4% of cases for N1, 3.5% of cases for P2, 6.0% of cases for N2, and 3.0% of cases for P3.

Evaluation of model waveform in relation to the average

In the normals, across all 15 sites, at the four latencies of the components as identified manually, the waveform difference values (real ERP minus model waveform sample values) were significantly different overall from their expected value of zero for N1 ($P = 0.030$, $F(15,10) = 3.34$), but not for P2, N2 or P3, on MANOVA (one-sample Hotelling's T^2 analysis). For the N1 component, this difference represented a smaller amplitude in the model waveform at all 15 electrode sites, the average global mean difference value being –0.63 μV. In the unmedicated and medicated schizophrenics, the difference values were not significantly different overall from zero for N1, P2 or N2, but for P3 they were significantly different overall in both groups, with $P = 0.016$ ($F(15,10) = 4.02$) for the unmedicateds, and $P = 0.025$ ($F(15,10) = 3.51$) for the medicateds. In both cases the model waveform had smaller P3 amplitude than the real ERP waveform, at 14 sites in the unmedicated and 15 sites in the medicated group, the average global mean difference values being 0.30 μV and 0.53 μV, respectively.

Between measure comparisons

In the normals, across all 15 sites, the two amplitude estimates differed significantly overall for P2 ($P < 0.0001$, $F(15,34) = 6.55$), N2 ($P < 0.0001$, $F(15,34) = 4.80$), and P3 ($P = 0.024$, $F(15,34) = 2.27$) on MANOVA (two-sample Hotelling's T^2 analysis). For all three components, this difference reflected a considerably larger amplitude of the Gaussian component in isolation (parameter A) compared to the conventional manually identified peak-to-baseline amplitude, the Gaussian measure being increased at every electrode site in all three cases. The average global mean P2 amplitude in normals was 0.49 μV for the conventional amplitude and 6.21 μV for the Gaussian parameter A estimate. The average global mean N2 amplitude in normals was –4.00 μV for the conventional amplitude and –7.58 μV for the Gaussian parameter A estimate. Finally, the average global mean P3 amplitude was 7.81 μV for the conventional and 10.56 μV for the Gaussian estimate.

In the unmedicated schizophrenics, the two amplitude estimates were significantly different overall for P2 ($P < 0.0001$, $F(15,34) = 9.37$)

and P3 ($P = 0.0055$, $F(15,34) = 2.86$). Once again, in both cases the Gaussian parameter *A* estimate was considerably larger than the conventional amplitude, being increased at all 15 sites for both components. The average global mean P2 amplitude was –0.64 μV for the conventional amplitude (keep in mind this amplitude is relative to a pre-stimulus baseline), and 5.41 μV for the Gaussian estimate. The average global mean P3 amplitude was 4.90 μV for the conventional amplitude and 9.24 μV for the Gaussian parameter *A* estimate.

In the medicated schizophrenics, only the P2 component showed a significant difference overall for the two amplitude estimates ($P < 0.0001$, $F(15,34) = 5.35$), once again representing larger Gaussian parameter *A* amplitudes than conventional amplitudes at all 15 electrode sites. The average global mean P2 amplitude in the medicated patients was 2.50 μV for the conventional amplitude and 6.86 μV for the Gaussian estimate.

Between group comparisons

N1

For the conventional N1 amplitude, the average global mean in normals was –8.58 μV, in unmedicated schizophrenics was –7.89 μV, and in medicated schizophrenics was –6.51 μV. The medicated schizophrenics were significantly different overall from the normals ($P = 0.035$, $F(15,34) = 2.12$), representing a decreased N1 amplitude in medicated patients at all 15 electrode sites. Medicated patients were also significantly different overall from unmedicated patients ($P = 0.042$, $F(15,34) = 2.04$), also representing a decrease at every electrode site in medicated subjects.

For the Gaussian parameter *A* amplitude estimate, the average global mean in normals was –9.66 μV, in unmedicated patients was –8.22 μV, and in medicated patients was –7.62 μV. However, none of the between group comparisons showed a significant difference overall for this measure.

P2

For P2, none of the between group comparisons for either amplitude measure yielded a significant difference overall. The average global mean P2 conventional amplitude was 0.49 μV in normals, –0.63 μV in unmedicated schizophrenics, and 2.50 μV in medicated patients. For the Gaussian parameter *A* estimate, the average global mean P2 amplitude in normals was 6.21 μV, in unmedicated patients was 5.41 μV, and in medicated patients was 6.86 μV.

N2

For N2 also, none of the between group comparisons yielded significant findings overall for either amplitude measure. The average global mean conventional N2 amplitude was –4.00 μV in normals, –6.04 μV in unmedicated schizophrenics, and –3.64 μV in medicated patients. The average global mean Gaussian *A* parameter amplitude was –7.58 μV in normals, –9.32 μV in unmedicated schizophrenics, and –7.62 μV in medicated patients.

P3

For the conventional P3 amplitude, the average global mean in normals was 7.81 μV, in unmedicated schizophrenics was 4.90 μV, and in medicated schizophrenics was 5.53 μV. The reduction in global mean P3 amplitude in unmedicated schizophrenics compared to normals was significant on *t*-test ($P = 0.039$, $t = 2.13$), and represented a decrease at every electrode site, but was not significant overall (with Hotelling's T^2-test). None of the other between group comparisons yielded a significant finding.

For the Gaussian *A* parameter amplitude, the average global mean in normals was 10.56 μV, in unmedicated schizophrenics was 9.24 μV, and in medicated schizophrenics was 7.96 μV. The situation was quite different from the conventional average results. Medicated schizophrenics had significantly reduced Gaussian P3 amplitude compared to normals, which was significant with both the global means on *t*-test ($P = 0.0013$, $t = 3.41$), and overall with Hotelling's T^2-test ($P = 0.033$, $F(15,34) = 2.13$). This represented a decreased P3 Gaussian amplitude in medicated patients at all 15 electrode sites compared to normals. Unmedicated patients, however, were not significantly different from normals either in regard to the global means or the overall Hotelling's T^2 analysis. Medicated patients also had significantly reduced overall Gaussian P3 amplitude compared to unmedicated schizophrenics ($P = 0.012$, $F(15,34) = 2.56$), representing a decrease at 12 of the 15 electrode sites. This difference

was not significant in relation to the global means.

In summary, a reduced N1 amplitude in medicated patients seen with the conventional measure was not seen with the Gaussian parameter *A* estimate. A reduced P3 amplitude in unmedicated patients with the conventional amplitude measure was not supported by the Gaussian estimate, but instead P3 amplitude was found with this measure to be reduced in the medicated patients.

Other findings

Figure 5 shows the graphs of P3 latency for all sites and subjects combined, in each of the three groups (these are the conventional latencies obtained by means of manual identification). There does not appear to be an obvious bimodal tendency in the distributions.

Figure 6 gives four examples where the modelling procedure did not perform adequately. In the first example (error 1 in the figure), the problem was due to the presence of a prominent P3a and P3b in the average waveform. Consequently, the Gaussian function that was intended to model the P2 component instead modelled P3a, and the Gaussian that was intended to model the P3 component modelled P3b. The N2 Gaussian modelled the negative part of the curve between P3a and P3b. In the second example (error 2), there was an unusual post-P3 positivity. The P3 Gaussian modelled this part of the curve instead of the P3 component. In the third example (error 3), the post-P3 negativity in the average (which was not uncommon) overlapped the N2 and P3 components, causing them to be considerably offset

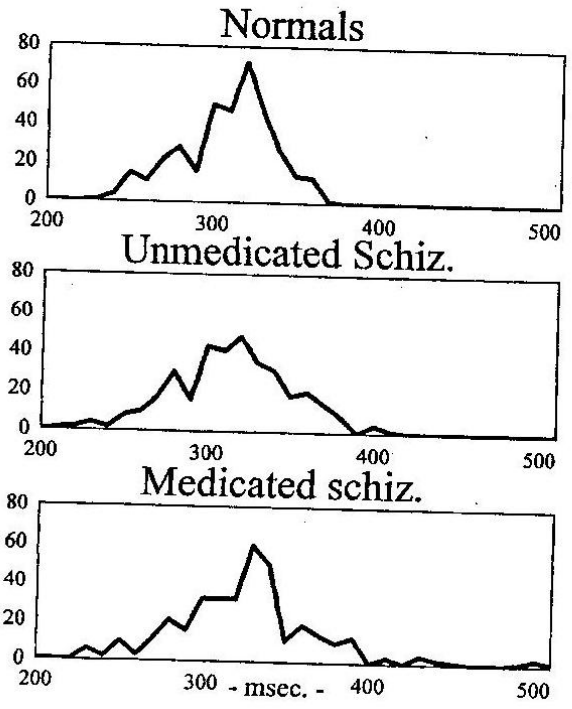

Figure 5 The distribution of P3 latencies (all sites and subjects combined) for each of the three groups of subjects. These are the conventional latencies as identified by a trained observer. There does not appear to be an obvious bimodal tendency in any of the distributions.

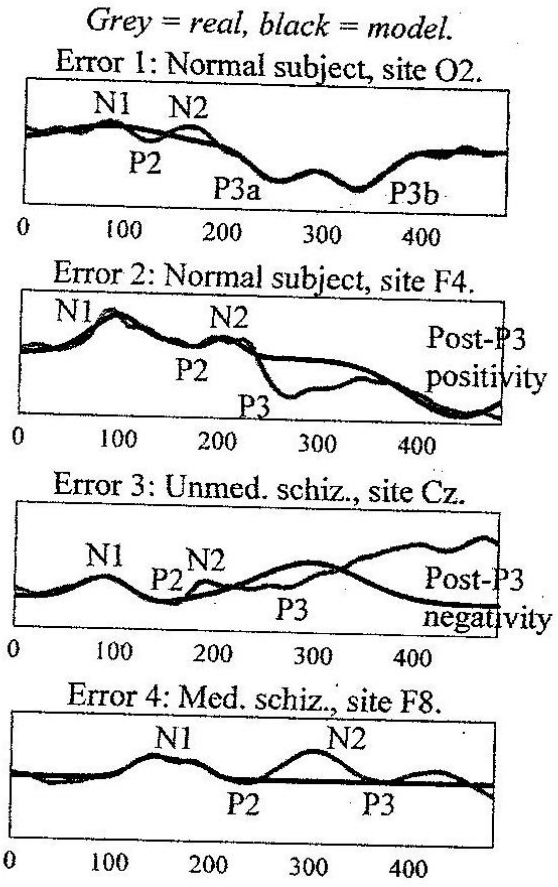

Figure 6 This figure shows four examples where the model produced erroneous results. In the first example, the problem was due to a prominent P3a and P3b in the waveform. In the second, the problem was due to an unusual post-P3 positivity. In the third, the problem was due to the post-P3 negativity overlapping the N2 and P3 components. In the fourth, the problem was due to the delayed latency of the components in the average, especially N2 which was delayed past 300 ms. Consequently, the model constraints prevented N2 and P3 from being appropriately modelled.

from the baseline. Consequently, the N2 and P3 Gaussians in the model waveform were quite wrongly positioned. In the fourth example (error 4), all of the components in the average are delayed in latency, and the N2 component in particular is delayed beyond 300 ms. Consequently, the constraints of the model prevented the N2 and P3 components of the waveform from being modelled. This is a (rare) example of inappropriate model constraints.

Discussion

This study set out to explore the possible role of component overlap in relation to the N1, P2, N2, and P3 component amplitude findings in schizophrenia, using a simple hypothesized model of the structure of the average ERP. The most important finding in relation to this model is the possibility that overlap is significantly affecting traditional peak-to-baseline estimates for all four components, particularly P2 and P3, but also N2, and to a lesser extent N1. Furthermore, these overlap effects, if they are real, seem to affect group ERP data in different ways.

These results seem to indicate that the model waveforms themselves reasonably represent the morphological structure of the real average ERPs, although some error is involved. Across the three groups, the component latencies were identified "correctly" in around five-sixths of cases for N1, two-thirds of cases for P2 and N2, and three-quarters of cases for P3. However, there is no reason we should necessarily expect the peak of the underlying component to occur at the same latency as the peak in the overall waveform, given the effects of component overlap, which may alter apparent latency as well as apparent amplitude. Although we have labelled the Gaussian latencies "incorrect" if they did not closely correspond to the latencies of the peaks in the overall waveform, they are not necessarily incorrect in reality, since the latency of peaks in the overall waveform may be distorted by component overlap. This is likely to account for most of the discrepancy in the latencies observed in this study between the Gaussian peaks and the real waveform peaks as identified manually, given the close morphological match between model and real waveforms. Although component latency was not the focus of this study, these results indicate that clinical studies of component latency, and not just studies of component amplitude, may be affected by the problem of component overlap.

Although the model waveform seems to be understating the amplitude of N1 in normals and P3 in patients in relation to the average waveforms, the error involved is small (on average less than or equal to $-0.63\,\mu V$), and some error must be expected given the simplicity of the Gaussian component shape. The best that can be hoped for at this stage is a reliable approximation rather than exactness. Some of the error in relation to P3 may be due to the presence of multiple subcomponents, since there is a hint of bifurcation in Figures 2 and 4 for the real grand averages (normals and medicated schizophrenics), although this is not borne out by the latencies (Figure 5). It should also be noted that a post-P3 negativity was present (Figures 2, 3 and 4) which was not taken into account by the model.

If it is accepted that component overlap of Gaussian-like components is occurring physically (rather than just mathematically), which has not been proven by this study, then it seems that traditional peak-to-baseline estimates of component amplitude, whether identified manually or automatically, are heavily contaminated by component overlap. The most significantly affected component is P2, which, while generally considered a small component, might in fact be a large amplitude component significantly affected by overlap, which results in partial cancellation. Similarly, N2 and P3 may be larger than peak-to-baseline estimates suggest, and even N1 may be affected somewhat, since the clinical findings in relation to N1 differed in relation to the two amplitude estimates.

A decreased N1 amplitude (conventional peak-to-baseline) has been reported in medicated or mainly medicated schizophrenics in a variety of auditory oddball ERP studies such as Barrett, McCallum, and Pocock (1986) and a number of studies have found that this N1 amplitude decrease was either exclusively found in medicated subjects (Pfefferbaum, Ford, White, & Roth, 1989) or was accentuated when patients were retested on medication (Blackwood et al., 1987). These findings are consistent with our results. However, the find-

ings in this study raise the possibility that this decreased N1 amplitude in medicated schizophrenics may be contributed to or due to component overlap effects, rather than reflecting a real decrease in amplitude of the underlying component.

The absence of significant findings in either clinical group in relation to the P2 component in this study is consistent with previous target auditory oddball ERP studies such as Roth, Horvath, Pfefferbaum, and Kopell (1980) and Blackwood et al. (1987). Similarly, no significant N2 findings occurred in auditory oddball studies by Brecher, Porjesz, and Begleiter (1987) and Romani et al. (1987), which is also consistent with our findings.

P3 amplitude reduction has been reported in numerous auditory oddball studies in both unmedicated and medicated patients (Baribeau-Braun, Picton, & Gosselin, 1983; Blackwood et al., 1987; Ebmeier et al., 1990; Ford et al., 1994; Kutcher, Blackwood, St. Clair, & Gaskell, 1987; Michie, Fox, Ward, Catts, & McConaghy, 1990; Pfefferbaum et al., 1989; Romani et al., 1987). In this study the decreased P3 amplitude in unmedicated patients seen with the conventional amplitude measure was not supported by the Gaussian parameter *A* estimate, which revealed instead a decreased P3 amplitude in the medicated patients. Again, this raises the possible role of overlap effects in relation to the interpretation of P3 amplitude findings, in terms of whether this finding relates primarily to the disease state or whether it is an effect of medication. The fact that the decreased conventional P3 amplitude in unmedicated schizophrenics was significant for the global means but not for Hotelling's T^2-test, would suggest that there was considerable variability in the topographic distribution of P3 within individuals in both groups, which would increase the variability in relation to Hotelling's T^2, but would tend to be eliminated by forming a global mean.

The results of this study do not prove that the model of four Gaussian components is correct, and must be interpreted cautiously. However, the large differences between the Gaussian parameter *A* amplitude measure and the traditional peak-to-baseline amplitude suggest such alternative interpretations are worth considering. This method provides one possible approach to begin to clarify component amplitude abnormalities in schizophrenia and to allow the association between the various components and postulated aspects of information processing to be analyzed without contamination by the effects of overlap.

Acknowledgments

We wish to thank Mr. John Anderson, Research Officer in the Department of Psychiatry, Westmead Hospital, for his role in collecting the data which was analyzed in this study.

Address correspondence to:

Albert Haig
41 Bridge St.
Waratah, N.S.W., 2298
Australia

References

American Psychiatric Association (1987). *DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., revised). Washington, DC: American Psychiatric Association.

Anderson, J., Rennie, C., Gordon, E., Howson, A., & Meares, R. (1991). Measurement of maximum variability within event related potentials in schizophrenia. *Psychiatry Research, 39*, 33–44.

Andreasen, N. C., & Olsen, S. (1982). Negative versus positive schizophrenia. *Archives of General Psychiatry, 39*, 784–794.

Baribeau-Braun, J., Picton, T. W., & Gosselin, J. Y. (1983). Schizophrenia: A neurophysiological evaluation of abnormal information processing. *Science, 219*, 874–876.

Barrett, K., McCallum, W. C., & Pocock, P. V. (1986). Brain indicators of altered attention and information processing in schizophrenic patients. *British Journal of Psychiatry, 148*, 414–420.

Blackwood, D. H., Whalley, L. J., Christie, J. E., Blackburn, I. M., St. Clair, D. M., & McInnes, A. (1987). Changes in auditory P3 event-related potential in schizophrenia and depression. *British Journal of Psychiatry, 150*, 154–160.

Blom, J. L., & Anneveldt, M. (1982). An electrode cap tested. *Electroencephalography and Clinical Neurophysiology, 54*, 591–594.

Brecher, M., Porjesz, B., & Begleiter, H. (1987). The N2 component of the event-related potential in schizophrenic patients. *Electroencephalography and Clinical Neurophysiology, 66*, 369–375.

Chatfield, C., & Collins, A. J. (1980 a). *Introduction to mul-*

tivariate statistics (pp. 57–81). London: Chapman & Hall.

Chatfield, C., & Collins, A. J. (1980 b). *Introduction to multivariate statistics* (pp. 114–139). London: Chapman & Hall.

Donchin, E., Tueting, P., Ritter, W., Kutas, M., & Heffley, E. (1975). On the independence of the CNV and the P300 components of the human averaged evoked potential. *Electroencephalography and Clinical Neurophysiology, 38*, 449–461.

Ebmeier, K. P., Potter, D. D., Cochrane, R. H., MacKenzie, A. R., MacAllister, H., Besson, J. A., & Salzen, E. A. (1990). P300 and smooth eye pursuit: concordance of abnormalities and relation to clinical features in DSM-III schizophrenia. *Acta Psychiatrica Scandinavica, 82*, 283–288.

Endicott, J., & Spitzer, R. L. (1979). Use of the research diagnostic criteria and the schedule for affective disorders and schizophrenia. *Journal of Nervous and Mental Disease, 171*, 34–39.

Ford, J. M., White, P., Lim, K. O., & Pfefferbaum, A. (1994). Schizophrenics have fewer and smaller P300s: A single trial analysis. *Biological Psychiatry, 35*, 96–103.

Gerson, J., Cardenas, V. A., & Fein, G. (1994). Equivalent dipole parameter estimation using simulated annealing. *Electroencephalography and Clinical Neurophysiology, 92*, 161–168.

Haig, A. R., Gordon, E., Rogers, G., & Anderson, J. (1995). Classification of single trial ERP sub-types: application of globally optimal vector quantization using simulated annealing. *Electroencephalography and Clinical Neurophysiology, 94*, 288–297.

Hunt, E. (1985). Mathematical models of the event-related potential. *Psychophysiology, 22*, 395–402.

Kirkpatrick, S., Gelatt, C. D., & Vecchi, M. P. (1983). Optimization by simulated annealing. *Science, 220*, 671–680.

Kutcher, S. P., Blackwood, D. H., St. Clair, D., Gaskell, D. F., & Muir, W. J. (1987). Auditory P300 in borderline personality disorder and schizophrenia. *Archives of General Psychiatry, 44*, 645–650.

Marsaglia, G. (1972). Choosing a point from the surface of a sphere. *The annals of mathematical statistics, 43*, 645–646.

McGillem, C. D., & Aunon, J. I. (1987). Analysis of event-related potentials. In A.S. Gevins & A. Rémond (Eds.), *Methods of analysis of brain electrical and magnetic signals* (pp. 131–169). Amsterdam: Elsevier.

Metropolis, N., Rosenbluth, A. W., Rosenbluth, M. N., Teller, A. H., & Teller, E. (1953). Equation of state calculations by fast computing machines. *Journal of Chemical Physics, 21*, 1087–1092.

Michie, P. T., Fox, A. M., Ward, P. B., Catts, S. V., & McConaghy, N. (1990). Event-related potential indices of selective attention and cortical lateralization in schizophrenia. *Psychophysiology, 27*, 209–227.

Möcks, J. (1986). The influence of latency jitter in principal component analysis of event-related potentials. *Psychophysiology, 23*, 480–484.

Möcks, J., & Verleger, R. (1986). Principal component analysis of event-related potentials: a note on misallocation of variance. *Electroencephalography and Clinical Neurophysiology, 65*, 393–398.

O'Connor, S. J., Simon, R. H., & Tasman, A. (1984). Model referenced method of evoked potential analysis. *Electroencephalography and Clinical Neurophysiology, 59*, 497–503.

Pfefferbaum, A., Ford, J. M., White, P. M., & Roth, W. T. (1989). P3 in schizophrenia is affected by stimulus modality, response requirements, medication status, and negative symptoms. *Archives of General Psychiatry, 46*, 1035–1044.

Press, W. H., Flannery, B. P., Teukolsky, S. A., & Vetterling, W. T. (1992). *Numerical recipes in C: The art of scientific computing* (2nd ed., pp. 394–455). Cambridge: Cambridge University Press.

Pritchard, W. S. (1986). Cognitive event-related potential correlates of schizophrenia. *Psychological Bulletin, 100*, 43–66.

Robins, L. N., Wing, J., & Hezler, J. (1987). *Composite International Diagnostic Interview*. Geneva: World Health Organisation.

Rogers, L. J. (1991). Determination of the number and waveshapes of event related potential components using comparative factor analysis. *International Journal of Neuroscience, 56*, 219–246.

Romani, A., Merello, S., Gozzoli, L., Zerbi, F., Grassi, M., & Cosi, V. (1987). P300 and CT scan in patients with chronic schizophrenia. *British Journal of Psychiatry, 151*, 506–513.

Roth, W. T., Horvath, T. B., Pfefferbaum, A., & Kopell, B. S. (1980). Event-related potentials in schizophrenics. *Electroencephalography and Clinical Neurophysiology, 48*, 127–139.

Verleger, R., & Wascher, H. E. (1995). Fitting ex-Gauss functions to P3 waveshapes: an attempt at distinguishing between real and apparent changes of P3 latency. *Journal of Psychophysiology, 9*, 146–158.

Wood, C. C., & McCarthy, G. (1984). Principal component analysis of event-related potentials: simulation studies demonstrate misallocation of variance across components. *Electroencephalography and Clinical Neurophysiology, 59*, 249–260.

Zeger, K., Vaisey, J., & Gersho, A. (1992). Globally optimal vector quantizer design by stochastic relaxation. *IEEE Transactions on Signal Processing, 40*, 310–322.

Appendix: Simulated annealing minimization

We can consider the 12 model parameters A_1 ... C_4 as constituting a vector in a 12 dimensional space, with each element of the vector being one of the parameters. We will call this the model parameters vector. The elements of this model parameters vector are initialized to some selected starting values at the beginning of the procedure. The process of simulated annealing involves repeatedly randomly perturbing this model parameters vector such that a new (perturbed) model parameters vector is created. The squared error of this new (perturbed) model parameters vector is computed. If the squared error is lower than the old model parameters vector, the old vector is discarded and the new (perturbed) model parameters vector takes its place. If the squared error has increased, then the perturbation may or may not be accepted on a chance basis. The probability of the perturbation being accepted is given by the following equation (Metropolis et al., 1953; Zeger, Vaisey, & Gersho, 1992):

$$p = e^{-\frac{\Delta E}{T}} \quad (4)$$

Here ΔE represents the increase in the squared error introduced by the perturbation, T is a "temperature" parameter, and p the probability of the perturbation being accepted. The greater the squared error introduced by the perturbation the less likely that perturbation is to be accepted, and the greater the temperature (the "hotter" the system) the more likely that perturbation is to be accepted.

The approach is to start the system at a high temperature when many perturbations are accepted, even ones that increase the squared error by a large amount, and wait for thermal equilibrium at this temperature, then to gradually reduce the temperature (the value of T), at each new T waiting for thermal equilibrium to occur. Once T becomes very low, few new perturbations will be accepted and the system has effectively become "frozen" at a solution. It is the ability of the Metropolis algorithm to climb "uphill," or to accept perturbations which increase the squared error, which allows it to escape from local minima.

The starting conditions consisted of allocating the first component a latency of 100 ms, an amplitude of –10.0 μV, and a width parameter of 25 ms (N1); the second component a latency of 180 ms, an amplitude of + 7.5 μV, and a width parameter of 20 ms (P2); the third component a latency of 240 ms, an amplitude of –7.5 μV, and a width parameter of 20 ms (N2); and the fourth component a latency of 300 ms, an amplitude of + 10.0 μV, and a width parameter of 25 ms (P3). These starting conditions, although in the correct order of magnitude, were arbitrary, but one of the features of simulated annealing is that the starting conditions quickly become irrelevant and do not affect the final solution. A vector having all its elements equal to these starting values is here termed the *starting vector*.

Each perturbation was performed according to the following procedure. An offset vector was computed, by first generating a 12-dimensional unit vector with uniformly random direction (Marsaglia, 1972). Each element of the offset unit vector was then multiplied by the corresponding element in the starting vector. This was necessary because the different parameters have quite different orders of magnitude (for instance, latency is in the order of 100 to 300 units, while amplitude is in the order of 10 units), and it was therefore necessary to weight the offset vector along each axis in proportion to the approximate magnitude of the particular parameter. This has the effect of selecting the offset vector randomly from the surface of a (12-dimensional) hyper-ellipsoid rather than the surface of a unit hyper-sphere, with the intersection of this hyper-ellipsoid with each axis occurring at the starting parameter value for that axis. In order that a given parameter should change by no more than 5% of its starting value in one perturbation, the length of the offset vector was then scaled by a factor of 0.05. A uniformly random number between 0 and 1 was then generated and the offset vector scaled by this amount. Finally, the new (perturbed) model parameters vector was computed as the sum of the offset vector and the old model parameters vector.

Once a perturbed model parameters vector had been computed, it was examined to ensure that all of the parameters were within certain constraints. If any of the parameters violated these constraints, another perturbed vector was generated using exactly the same method, this process being repeated until a vector in which all the parameters satisfied the constraints was produced. By this means the per-

turbed vectors used in the simulated annealing procedure always adhered to the constraints. These were as follows. The first Gaussian component (modelling N1) had to be within the latency window 60 to 180 ms. The second Gaussian component (modelling P2) had to be within 110 to 260 ms, the third Gaussian component (N2) had to be within 140 to 300 ms, and the fourth (P3) had to be within 240 to 450 ms. The components had to occur in this order (that is, N1 had to precede P2, P2 had to precede N2, and N2 had to precede P3). Each Gaussian component had to have a latency greater than the preceding one by at least 20 ms. This prevented negligible deviations being modelled by two large components of opposite sign with almost identical latencies. The first Gaussian had to have negative amplitude, the second positive, the third negative, and the fourth positive. Finally, the width parameter (C) for each component had to be greater than 15 and less than 75 ms (the total duration of a component from 0.368 ($1/e$) of the peak amplitude before the peak to 0.368 of the peak amplitude after the peak could not be less than 30 ms or exceed 150 ms).

The simulated annealing procedure was then carried out as follows (parameters marked with a superscript 1 were obtained from Zeger et al., 1992, as based on Kirkpatrick et al., 1983, and parameters marked with a superscript 2 were arrived at by means of experimentation). The process was started at a value of T (T_0), the temperature parameter, at which at least 25%[1] of perturbations were accepted. At each temperature, thermal equilibrium was considered to have been reached either after 1000[2] *accepted* perturbations, or if after 10000[2] *attempted* perturbations the squared error had changed by less than 0.1%[1]. The temperature parameter was then reduced to the next value in the temperature schedule, which was given by the following equation (Zeger et al., 1992):

$$T_n = T_0 \bullet K^n \qquad (5)$$

The value of K was set to 0.9[1]. The system was run until either at a given temperature less than 0.1%[1] of perturbations were accepted, or the squared error changed for the last five[2] temperature iterations by less than 0.1%[1]. The system was then considered "frozen" at the solution.