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Abstract

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Methods. EEGs were recorded for 40 subjects with schizophrenia and 40 age and sex matched controls during an auditory oddball reaction time task. ERPs to the targets and non-targets immediately preceding the targets were averaged separately.

Results. There was a disturbance in ERPs to targets but also to non-targets (reduced N100 amplitude and earlier P200 latency) and the difference between target and non-target ERP components (N100 and P200 amplitude and P200 latency), was significantly reduced in the schizophrenic group compared with controls.

Conclusions. These findings suggest a disturbance in processing task relevant and irrelevant stimuli, consistent with Gray’s (1998) hypothesis of misattributions in the ‘match[ratio]mismatch’ of novel (target) and familiar (non-target) sensory input compared with stored information.

Disciplines
Arts and Humanities | Life Sciences | Medicine and Health Sciences | Social and Behavioral Sciences

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misattribution of sensory input reflected in dysfunctional target:non-target ERPs in schizophrenia

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ABSTRACT

Background. While numerous studies have found disturbances in the Event-Related Potentials (ERPs) of patients with schizophrenia linked to task relevant target stimuli (most notably a reduction in P300 amplitude), few have examined ERPs to task irrelevant non-targets. We hypothesize, from current models of dysfunction in information processing in schizophrenia, that there will be less difference between ERPs to targets and non-targets in patients with schizophrenia than in controls.

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Conclusions. These findings suggest a disturbance in processing task relevant and irrelevant stimuli, consistent with Gray’s (1998) hypothesis of misattributions in the ‘match:mismatch’ of novel (target) and familiar (non-target) sensory input compared with stored information.

INTRODUCTION

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, 1998a; Gray et al. 1991; Hemslay, 1996) propose a core physiological mechanism underlying this process, namely a disturbance of the comparator process in the hippocampus, 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). This model is consistent with Sokolov’s (1963; Sokolov & Vinograda, 1975) neuronal model and with aspects of the models proposed by Andreasen et al. (1998); Frith et al. (1992) and Servan-Schreiber et al. (1996), suggesting a disruption in the monitoring of willed intention, a failure in the inhibitory effect of context and a

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deficit in the coordination and expression of information, respectively.

Event-related potentials (ERPs), acquired during an auditory oddball task, offer a window into the neurophysiological processing of cognitive events on a fraction of a second time-scale. The suggested time span of the ‘match:mismatch’ comparator is approximately 80–160 ms after the stimulus (Gray, 1998). The late component ERPs have been associated with different aspects of information processing. The N100 is thought to reflect aspects of attentional processes (Hillyard & Picton, 1987), P200 reflects aspects of decision making or stimulus encoding (McCarley et al., 1991), N200 is associated with response selection (Snyder & Hillyard, 1976) and P300 with context updating (Donchin et al., 1986) and context closure (Verleger, 1988). N100 and P200 might be expected to reflect aspects of processing before (N100) or at (P200) the putative comparator stage, and N200/P300 might reflect post-comparator processes.

While there has been an extensive literature on differences in ERPs between patients with schizophrenia and normal populations on the auditory oddball task, most previous late component ERP studies have examined responses to targets only, and the most replicated of these findings is decreased P300 amplitude (Pfefferbaum et al., 1989). Few previous studies have reported data from both targets and non-targets in schizophrenia. Reported findings include reduced N100 amplitude (Roth et al., 1980; Pfefferbaum et al., 1989) and both increased (Pfefferbaum et al., 1989) and reduced (Roth & Cannon, 1972; Roth et al., 1980) P200 amplitude. An interesting single-trial study (Roschke et al., 1996), which investigated the P300 component of both target and non-target ERPs, found that schizophrenics had fewer P300s to targets and more P300s to non-targets than normal controls, which suggests that the disturbance may lie in the discrimination between targets and non-targets. This study served to examine further the possible extent of the disturbance in target and non-target processing reflected in ERPs. In addition, rather than limiting assessment to a disturbance in ERPs to targets or non-targets we also examined the difference between the ERP responses to target and non-target stimuli.

METHOD

Subjects

Forty subjects 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, and 40 age and sex matched non-psychiatric control subjects (mean age 36–7 years, range 20 to 54 years) were drawn from the general population. The mean chlorpromazine equivalent for medication in the subjects with schizophrenia was 660 ± 636.6. Exclusion criteria for both groups were 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 (CIDI) (World Health Organization, 1990) and the Westmead Hospital Clinical Information Base questionnaire (WHCIB). Diagnosis of schizophrenia was confirmed using CIDI sections (relating to depression, mania, schizophrenia and other psychotic disorders) according to DSM-III-R criteria (American Psychiatric Association, 1987). After interview, schizophrenic symptoms were rated using the Positive and Negative Syndrome Scale (PANNS) (Kay & Opler, 1987). Control subjects were also screened for history of psychiatric illness (themselves or first-degree relative). The WHCIB was also used to obtain demographic information for both groups.

Data acquisition

Subjects 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 dBSPL and the interstimulus interval (ISI) was 1.3 s. Subjects were asked to look at a dot on the computer screen 60 cm in front of them, ignore the low (background) task irrelevant 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. ‘Speed and accuracy of response’ were emphasized equally. EEGs were recorded.
on a DC based system (Synamps) from 19 scalp sites (F8, T4, T6, Fp2, F4, C4, P4, O2, Fz, Cz, Pz, Fpl, F3, C3, P3, O1, F7, T3 and T5) 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 digitized at 250 Hz. Horizontal 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). Thereafter, averaged ERPs to target stimuli were computed and N100, P200, N200 peaks were measured relative to a prestimulus (200 ms) baseline by an automated system (to avoid the possibility of observer bias) 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 et al. 1995) with the criteria that N100 occurred between 80–140 ms, P200 between 150–200 ms, N200 between 200–280 ms and P300 between 250–500 ms after the Gratton EOG correction procedure. Averaged ERPs to non-targets were computed from the 40 non-targets preceding each target stimuli, and N100, P200 peaks were ascertained according to the same method (except that P200 occurred between 160–240 ms.

**Analysis**

Non-target ERP components, (N100 and P200) and target ERP components (N100, P200, N200, P300) amplitude and latency were first submitted separately to a three-way MANCOVA with the between group factor of group (schizophrenic vs. controls) and the within-subject factors of site (Fz, Cz, Pz), and condition (target vs. non-target), and CPZ equivalents as the covariate, using SPSS 9.0. MANOVA (SPSS Inc., 1999) results were subsequently interpreted with any effects of medication taken into account.

In addition, difference scores for N100 and P200 ERP components were assessed by subtracting non-target amplitude and latency from target amplitude and latency. The difference scores were also analysed using three-way mixed design, repeated measures MANCOVA as above.

**RESULTS**

ERP waveforms for the target and non-target schizophrenic and normal groups are shown in Figs. 1 and 2(a). Difference (between target and non-target) scores for patients with schizophrenia and controls are shown in Fig. 2(b). Means and standard deviations for each component amplitude and latency appear in Table 1. Medication effects (CPZ equivalents) could not account for any significant between group differences (CPZ equivalents did not significantly covary with any of these differences). There were significant group by condition by site interactions at N100 amplitude (F = 11.45; df = 2,75; P < 0.000). P200 amplitude (F = 7.60; df = 2,75; P < 0.001) and P200 latency (F = 5.19; df = 2,75; P = 0.008).

**Targets**

Patients with schizophrenia showed significantly smaller N100 amplitudes than normal controls at Fz (F = 5.25; df = 1.74; P = 0.025) Cz (F = 7.47; df = 1.74; P < 0.008) and Pz (F = 4.37; df = 1.74; P < 0.040). P200 amplitudes were significantly larger than controls at Cz (F = 11.49; df = 1.74; P = 0.001); N200 amplitudes were significantly smaller than controls at Cz (F = 6.62; df = 1.61; P < 0.013) and P300 amplitudes were significantly smaller than normal controls at Fz (F = 5.76; df = 1.69; P = 0.019). In patients with schizophrenia P200 latency was significantly later than controls at Cz (F = 4.92; df = 1.74; P = 0.03) and Pz (F = 4.06; df = 1.74; P = 0.047) and N200 latency was significantly later than controls at Cz (F = 4.92; df = 1.74; P = 0.03) and Pz (F = 4.06; df = 1.74; P = 0.047).

**Non-targets**

N100 amplitudes for patients with schizophrenia were significantly smaller than controls at Cz (F = 12.76; df = 1.74; P = 0.001) and Pz (F = 10.14; df = 1.74; P = 0.002). P200 latency was also significantly earlier than for controls at Cz (F = 11.89; df = 1.74; P = 0.001) and Pz (F = 5.54; df = 1.74; P = 0.021). Both patients with schizophrenia and normal controls had the same
Fig. 1. The superimposed group average ERPs of the schizophrenic group (— —— ) and normal controls (———) at midline sites. Compared with controls, patients with schizophrenia showed reduced N100 amplitude and earlier P200 latency to non-targets and decreased N100, N200 and P300 amplitude (but increased P200), as well as delayed P200 and N200 latency in response to targets.

Direction in within subject results between targets and non-targets for amplitude i.e. N100 amplitudes were larger for targets than non-targets, and P200 amplitudes for targets were equal to or smaller than non-targets. However, for P200 latency (Cz and Pz) the patient group is delayed in processing speed, compared with controls, for targets, but earlier in processing speed, than controls, for non-targets.

Targets minus non-targets

Patients with schizophrenia had significantly smaller amplitude difference scores at Fz for N100 amplitude \( (F = 7.54; \text{df } = 1.75; \text{P } = 0.008) \) and at Cz for P200 \( (F = 4.74; \text{df } = 1.75; \text{P } = 0.032) \) components than normal controls. They also had significantly smaller latency difference scores than controls for P200 at Cz.
Dysfunctional target: non-target ERPs in schizophrenia

**DISCUSSION**

This study examined differences in ERP components evoked in response to targets and non-targets in patients with schizophrenia and age and sex matched controls. Consistent with previous literature that focused on processing task relevant target stimuli, the patient group showed a decrease in N100 amplitude (associated with attention) and increased P200 amplitude and delayed latency (associated with decision making), delayed N200 latency (associated with response selection) and diminished P300 amplitude (associated with the context of information processing).

Few studies have, however, additionally examined the non-target stimuli. In this study, non-target ERPs in the patient group showed a decreased N100 amplitude and earlier P200 latency, compared with controls.

The pattern of ERP response in the patient group therefore, was first 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 might suggest that for non-target stimuli there was a premature closure of decision making (reflected in earlier P200 latency), whereas for
target stimuli there was increased network activation (reflected by increased amplitude) and a consequent delayed speed of processing (reflected in P200 latency) in the patient group.

A disturbance in target:non-target discrimination is further suggested by the difference waveform analysis (target minus non-target ERPs, see Fig. 2(b)), which showed that the targets and non-targets were processed in a more similar fashion in the patient group (compared with the controls), and the difference waveform was markedly reduced (particularly for 150–250 ms) in the patient group.

This disturbance in the processing of target and non-target information is consistent with Roschke’s (Roschke et al. 1996) single trial P300 findings and with Gray’s (Gray et al. 1991) model in which misattributions in the ‘match:mismatching’ (in the subiculum of the hippocampus) 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 (Bahramali et al. 1998) and the decrease in processing the context of target information (as reflected in numerous studies by decreased P300 amplitude). This would be consistent with Broadbent’s (1958) suggestion that early stages of processing may lead downstream 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 & 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 (1998a, b), 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

<table>
<thead>
<tr>
<th>Target</th>
<th>Fz Control</th>
<th>Patient</th>
<th>Cz Control</th>
<th>Patient</th>
<th>Pz Control</th>
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<tr>
<td>Amp</td>
<td>–9.4 ± 3.1</td>
<td>–6.6 ± 3.3</td>
<td>–10.9 ± 3.9</td>
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<tr>
<td>Lat</td>
<td>108 ± 10.9</td>
<td>107 ± 16.2</td>
<td>105 ± 9</td>
<td>100 ± 11</td>
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<td></td>
</tr>
<tr>
<td>Amp</td>
<td>18 ± 4.1</td>
<td>40 ± 4.4</td>
<td>67 ± 4</td>
<td>48 ± 5</td>
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<tr>
<td>Lat</td>
<td>171 ± 17.0</td>
<td>173 ± 16.7</td>
<td>169 ± 16.3</td>
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<td>161 ± 19.0</td>
<td>175 ± 20.0</td>
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<tr>
<td>Amp</td>
<td>–46 ± 4.1</td>
<td>–50 ± 4.5</td>
<td>–79 ± 5.7</td>
<td>–3.3 ± 5.6</td>
<td>–485 ± 40</td>
<td>–21 ± 49</td>
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<tr>
<td>Lat</td>
<td>217 ± 19.0</td>
<td>223 ± 28.1</td>
<td>208 ± 17.1</td>
<td>227 ± 22.6</td>
<td>204 ± 23.7</td>
<td>231 ± 25.0</td>
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<tr>
<td>Amp</td>
<td>113 ± 5.7</td>
<td>7.3 ± 50</td>
<td>122 ± 7.0</td>
<td>11.3 ± 5.4</td>
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<tr>
<td>Lat</td>
<td>317 ± 28.0</td>
<td>326 ± 33.8</td>
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<tr>
<td>Amp</td>
<td>–8.6 ± 2.7</td>
<td>–8.6 ± 2.8</td>
<td>–10.1 ± 3.2</td>
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<tr>
<td>Lat</td>
<td>103 ± 17.3</td>
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<tr>
<td>Amp</td>
<td>40 ± 3.1</td>
<td>38 ± 3.1</td>
<td>63 ± 3.7</td>
<td>64 ± 2.9</td>
<td>37 ± 2.9</td>
<td>40 ± 2.2</td>
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<tr>
<td>Lat</td>
<td>199 ± 29.5</td>
<td>200 ± 29.4</td>
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<td>36 ± 32</td>
<td>84 ± 8</td>
<td>87 ± 9.3</td>
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<td>108 ± 10.3</td>
<td>164 ± 15.2</td>
<td>85 ± 5.4</td>
<td>87 ± 9.3</td>
<td>111 ± 10.2</td>
<td>163 ± 18.4</td>
</tr>
</tbody>
</table>

Table 1. Mean and standard deviation amplitudes and latencies for all components (target, non-target and difference scores) at midline sites
novel stimuli activate the cingulate and exploratory processing networks.

These psychophysiological findings may also be linked to disturbances in neurochemistry. There is a body of evidence linking dopamine hyperactivity to schizophrenia. 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 & Morrison, 1987; Cohen & Servan-Schreiber, 1993) and Dextro-amphetamine (indirect monoamine agonist) has been found to ‘focus’ neural activity that is specific for a particular task (Mattay et al. 1996).

In summary, this study draws attention to the potential existence and significance, of disentangling task relevant and task irrelevant processing dysfunction in schizophrenia. However, associations between the findings in this study (disturbances in non-target and target ERPs), and models that propose misattribution of these processes (Gray, 1998), neurochemical abnormalities (Mattay et al. 1996), network dysfunction (Posner & Dehaene, 1994), or disturbed interactions (Broadbent, 1958), are preliminary and indirect.

REFERENCES


