ERP amplitude and latency in breast cancer survivors treated with adjuvant chemotherapy

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Abstract

Objective: Neurocognitive problems that were observed in a number of breast cancer survivors treated with adjuvant chemotherapy initiated a series of EEG studies to examine the neurophysiological basis of these deficits. The aim of the present study was to examine the effects of various regimens of adjuvant chemotherapy on the N1 and P3 component of the event-related potential (ERP) in breast cancer patients 3–6 years after treatment.

Methods: Fifty-three breast cancer patients treated with various chemotherapy regimens were compared to 23 stage I breast cancer patients not treated with chemotherapy. An auditory oddball task was used to study the amplitude, latency and structure of the potential field of the N1 and P3.

Results: Patients treated with chemotherapy showed lower P3 amplitudes than patients not treated with chemotherapy. Differences were also observed in P3 latency between patients treated with different chemotherapy regimens.

Conclusions: Our results indicate a general effect of all chemotherapy regimens under study on P3 amplitude and a more specific chemotherapeutic effect on P3 latency.

Significance: The present study provides evidence for the notion that different chemotherapy regimens have different effects on brain functioning.

Keywords: Adjuvant chemotherapy; Breast cancer; Long-term side effects; Neurotoxicity; Cognitive deficits; Event-related potentials

1. Introduction

Cognitive deficits are found in a number of breast cancer patients treated with adjuvant chemotherapy in several neuropsychological studies (Van Dam et al., 1998; Schagen et al., 1999, 2006; Brezden et al., 2000; Ahles et al., 2002; Castellon et al., 2004; Wefel et al., 2004; Falleti et al., 2005; Schagen et al., 2006). This finding has initiated a series of studies to examine neurophysiological correlates of cognitive functioning in breast cancer patients treated with adjuvant chemotherapy. Adjuvant therapy refers to additional treatment given after a main mode of therapy (surgery). Schagen et al. (2001) administered...
a simple oddball task and measured EEG-derived event-related potentials (ERPs) in high-risk breast cancer patients assigned randomly to either standard-dose cyclophosphamide, epirubicin and fluorouracil (FEC) chemotherapy or high-dose chemotherapy, in which the latest cycle is replaced by cyclophosphamide, thiotepa and carboplatin (CTC), as well as in stage I breast cancer patients not treated with chemotherapy. ERPs allow analysis of the timing, duration and organisation of processes occurring in the brain during task performance. In the Schagen et al. study, P3 latency was assessed, which is related to the duration of stimulus-evaluation processes (Van der Molen et al., 1991). A significant relation was found between the latency of the P3 and the total number of deviant neuropsychological test scores per patient. It thus seems that neuropsychological impairments are related to a slowing of stimulus evaluation.

In the present study, we sought to extend these findings by also examining patients treated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy, next to patients randomly assigned to either a standard-dose or a high-dose regimen, like in the study mentioned above (Schagen et al., 2001). The inclusion of different groups is of interest as different chemotherapy regimens may have different effects on cognitive and brain functioning. Compared to the Schagen et al. study, a number of methodological refinements were made. Whereas in the previous study only P3 latency was assessed, in the present study P3 amplitude was also calculated. In two other studies employing a more complex information processing paradigm, P3 amplitude reductions were found for several chemotherapy regimens (Kreukels et al., 2005, 2006). These findings can be interpreted as a less intense stimulus-evaluation induced by chemotherapy. We were interested if this P3 amplitude reduction would also be apparent for different chemotherapy regimens in the simpler oddball paradigm. This would imply that aberrant stimulus-evaluation is common for several chemotherapy regimens across several simple and more complex cognitive functions and may thus reflect a basic impairment due to chemotherapy. Next to P3, we also studied amplitude and latency of the N1 component in these patients. The N1 component is related to early perceptual processing (Kok, 1997). We examined the latency of the N1 component to determine if a decrease in P3 latency is associated with a decrease in N1 latency. If this is the case, it would imply that this decrease is associated with changes in very early sensory processing.

2. Methods

2.1. Patients

Four groups of disease-free breast cancer survivors participated in the current cross-sectional study approximately 3–6 years posttreatment (see Table 1 for treatment characteristics). In the remainder of this article the patients will be mentioned by their group name as depicted in the last column of Table 1.

The patients were recruited from a database of a prospective neuropsychological study performed in the Antoni van Leeuwenhoek Hospital/Netherlands Cancer Institute (Amsterdam, The Netherlands). The study was approved by the institutional review board. Patients had to fulfill the following inclusion criteria: (1) no presence of metastatic disease or relapse; (2) no history of neurological or psychiatric signs that might lead to deviant test results; (3) no use of medication that might lead to deviant test results; (4) no alcohol or drug abuse; and (5) sufficient command of the Dutch language. Written informed consent was obtained from all participants according to institutional guidelines.

### Table 1

<table>
<thead>
<tr>
<th>Treatment characteristics</th>
<th>Chemotherapy</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk breast cancer patients</td>
<td>Standard-dose regimen</td>
<td>FEC group</td>
</tr>
<tr>
<td>&lt;56 years with at least four tumor-positive axillary lymph nodes. Multicentre randomized trial (Rodenhuis et al., 2003) randomly assigned to either conventional-dose adjuvant treatment or high-dose treatment*</td>
<td></td>
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<tr>
<td>5x FEC</td>
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<tr>
<td>5-Fluorouracil, 500 mg/m²</td>
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<tr>
<td>Epirubicin, 90 mg/m²²</td>
<td></td>
<td></td>
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<tr>
<td>Cyclophosphamide, 500 mg/m²²</td>
<td></td>
<td></td>
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<tr>
<td>High-dose regimen</td>
<td>CTC group</td>
<td></td>
</tr>
<tr>
<td>4x CTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil, 500 mg/m²²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epirubicin, 90 mg/m²²</td>
<td></td>
<td></td>
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<tr>
<td>Cyclophosphamide, 500 mg/m²²</td>
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### Lymph-node positive breast cancer patients

<table>
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<tr>
<th>Group</th>
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<tbody>
<tr>
<td>6x CMF group</td>
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<tr>
<td>Cyclophosphamide 100 mg/m² orally on days 1–14</td>
</tr>
<tr>
<td>Methotrexate 40 mg/m²² intravenously on days 1 and 8</td>
</tr>
<tr>
<td>5-Fluorouracil 600 mg/m²² intravenously on days 1 and 8</td>
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</tbody>
</table>

### Stage I breast-cancer patients

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<tr>
<th>Group</th>
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<tbody>
<tr>
<td>None</td>
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</table>

All patients underwent surgery and received locoregional radiotherapy.

* Treated with tamoxifen (40 mg daily) for 2 years, and for 5 years when they had hormone-receptor positive cancer.
2.2. Study measures

2.2.1. Electrophysiological recording

Participants were examined at the Department of Clinical Neurophysiology of the Slotervaart Hospital (Amsterdam, The Netherlands) in a semi-dark sound-proof room. The electroencephalogram (EEG) was recorded with a 32-channel tin-electrodes Quikcap (Neuroscan) referenced to the left mastoid. Eye movements were recorded from bipolar tin-electrode pairs placed above and below the left eye, and left and right of the outer canthi of both eyes (Electro-oculogram, EOG). AFz served as a ground electrode. Impedances were kept below 5 kΩ. The EEG signals were amplified by a SynAmps amplifier (Neuroscan).Signals were recorded for a 2048 ms period starting 200 ms before stimulus presentation, digitized at 250 Hz, and bandpass filtered between 0.15 and 40 Hz.

2.2.2. Oddball task

The auditory oddball task is a commonly used and well-evaluated paradigm in experimental as well as clinical settings, to study brain potentials in response to standard and deviant tones. Participants were instructed to keep a mental count of the rare stimulus, a 2000 Hz tone presented with a probability of 20% and to report their count at the end of the test. Standard 1000 Hz tones were presented with a probability of 80%. All tones (250) were presented for 30 ms, rise and fall time 5 ms, at an intensity level of 75 dB with an inter-stimulus-interval (ISI) of 2 s using loudspeakers. Loudspeakers were calibrated using a dB meter at a 75 dB intensity level at the place where the patient is seated.

In the same experimentation session patients also completed several questionnaires, and EEG was registered in eyes open and eyes closed conditions and during an information processing task (AFM task). This task was part of another study, and data from this task have been published separately (Kreukels et al., 2005, 2006). The experimentation session lasted two and a half hours including electrode positioning and removal.

2.3. Electrophysiological data processing and analysis

Scan 4.2 software was used for off-line data processing. Three minutes of EEG and EOG was recorded while patients fixated on a cross in the centre of a computer screen to measure spontaneous eye blinks. This file was used to compute an average blink for each patient individually. From this average, transmission coefficients were computed by estimating the covariance of the averaged blink separately for all EEG channels. Then, the EOG was subtracted from the EEG channels on a sweep-by-sweep, point-by-point basis, incorporating the transmission coefficients (Semlitsch et al., 1986). EEG epochs that contained extensive horizontal eye movements or contained voltages in excess of plus or minus 100 µV were excluded. EEG epochs for each participant were then averaged for standard and deviant tones and aligned to a baseline (i.e., the average amplitude during the 200 ms preceding stimulus presentation was subtracted from each signal).

Data were rereferenced against the average reference and the global field power (GFP) was calculated (Hamburger and vd Burgt, 1991). GFP is a measure defined as the standard deviation across all channels as a function of time within a sample interval. GFP is used to quantify the instantaneous global activity across the spatial potential field sampled over the scalp. The result of this analysis is a waveform that represents the temporal changes in GFP. A peak of GFP at some point in time is thought to reflect a maximum (and a trough is thought to represent a minimum) of the total underlying brain activity that contributes to the surface potential field (Lehmann and Skrandies, 1980; Hamburger and vd Burgt, 1991). The GFP averaged over all participants was used to determine the segment in which the N1 and P3 were appreciated. The latency of the N1 and the P3 component was measured to the apex of the highest peak in the GFP in a segment between 70 and 130 ms and between 260 and 420 ms post-stimulus, respectively. The N1 and P3 amplitude were measured by calculating the total amplitude from peak to trough at the moment of maximal GFP in the designated segments. All electrode positions were described by their x- and y-axis co-ordinates. The peak and trough were located using this matrix. x- and y-co-ordinates of the peaks and troughs are the major landmarks that describe the principal structure of the potential field. Mean x- and y-values were calculated for the different treatment groups.

2.4. Statistical analysis

The Statistical Package for Social Sciences (SPSS) 12.0 software was used for all statistical analyses. Differences in patient and demographic characteristics between groups were analyzed by \( \chi^2 \) tests and univariate analysis of variance (ANOVA).

With regard to the oddball task, number of deviant tones counted, amplitudes and latencies of the N1 and P3 component, and the x- and y-co-ordinates of the peaks and troughs were entered in an ANOVA. Between-group comparisons were performed to study differences between the different treatment groups. To correct for the cumulative type I error, we used Keppel’s modified Bonferroni procedure (Keppel, 1991). The family-wise error rate was divided by the number of comparisons to determine the alpha level for each test. Accordingly, the \( p \)-value was determined at .0238 for each test.

We were primarily interested in the effects of the separate treatment regimens on the outcome measures. However, we also examined the overall effect of chemotherapy, that is the effect independent of treatment regimen, on the neurophysiological measures under study. Independent samples \( t \)-tests were used to examine if there were differences in N1 and P3 amplitudes, latency and co-ordinates between patients treated with chemotherapy and patients not treated with chemotherapy. To test for possible effects
of tamoxifen use on latency and amplitude on GFP, current, past and never users were compared in the CMF group. This group was chosen, because it was relatively large and comprised of sufficient users and not users to allow for meaningful analysis.

3. Results

3.1. Patients

One hundred and twenty-five patients were eligible for this study (23 FEC, 17 CTC, 46 CMF and 39 control patients). Thirty-seven patients (29.6% of the total group: 5 FEC, 2 CTC, 17 CMF and 13 control patients) declined from participating in the neurophysiological study. Reasons for withholding participation were: lack of interest, too busy, uncomfortable with EEG examination, and participation in other studies. Additionally, four patients could not be traced and six patients cancelled their appointment. Non-participants did not differ from participants in age and education.

The final study population consisted of 78 patients. Two more patients of the CMF group had to be excluded from further analysis due to technical problems. Sociodemographic and clinical characteristics of these patients are presented in Table 2.

There were no statistically significant differences between the four groups with regard to age and education level. CMF patients differed significantly in time since treatment from all other groups and were off treatment well over 1 year longer than the other patients. All patients were peri- or postmenopausal except for four control patients and one patient in the CMF group. In CTC and FEC chemotherapy groups all patients were past or current tamoxifen users, while in the CMF group half of the patients were current or past tamoxifen users and in the control group only two patients were treated with tamoxifen (see Table 2).

3.2. Performance differences

No differences were observed in the number of tones counted between the treatment groups \(F(3,74) = 1.866; p = .143\). Only three patients missed one or two tones. Fifty deviant tones were presented in the oddball task. The mean number of tones counted in all patients was 50.4 (SD = 1.2).

3.3. Original ERP waveforms

Fig. 1 shows the original ERP waveforms for different treatment regimens at electrode location Pz (see Fig. 1).

3.4. N1 and P3 latency

The latencies in the N1 and P3 segment at which the Global Field Power (GFP) reached its maximum are depicted in Table 3.

No significant differences were observed in latency of the GFP between the treatment groups in the N1 segment \(F(3,72) = 1.024; p = .387\). The effect of treatment on P3 latency was marginally significant \(F(3,72) = 2.268; p = .088\). Between-group comparisons revealed a significant mean difference in P3 latency between the CMF patients and the CTC patients of 40 ms with a \(p\)-value of

Table 2
Sociodemographic and clinical characteristics of the study patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient groups</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEC group ((N = 17))</td>
<td>CTC group ((N = 12))</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)*</td>
<td>51.2 (5.9)</td>
<td>51.5 (5.6)</td>
</tr>
<tr>
<td>Range</td>
<td>44–59</td>
<td>40–58</td>
</tr>
<tr>
<td>Time since treatment (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.1 (.7)</td>
<td>3.7 (.8)</td>
</tr>
<tr>
<td>Range</td>
<td>2.9–5.1</td>
<td>2.7–5.3</td>
</tr>
<tr>
<td>Education b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>6 (35.3%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Middle</td>
<td>6 (35.3%)</td>
<td>3 (25.0%)</td>
</tr>
<tr>
<td>High</td>
<td>5 (29.4%)</td>
<td>8 (66.7%)</td>
</tr>
<tr>
<td>Menopausal status c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Perimenopausal</td>
<td>2 (11.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>15 (88.2%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current user</td>
<td>13 (76.5%)</td>
<td>8 (66.7%)</td>
</tr>
<tr>
<td>Past user</td>
<td>4 (23.5%)</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td>Never user</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* SD, standard deviation.
 b Low, primary school; middle, secondary school; and high, university and graduate school.
 c Premenopausal, menstruating regularly during past 12 months; perimenopausal, menstruated during the past 12 months, but experiencing changes in the menstrual cycle length and menstrual irregularity; and postmenopausal, amenorrhea for at least 12 months.
.023. The mean difference between the CMF group and the control group was 28 ms with a p-value of .054. Independent samples t-test did not reveal differences in co-ordinates of the N1 or P3 between all patients treated with chemotherapy (independent of treatment) and patients not treated with chemotherapy. Within the CMF group, tamoxifen use did not significantly influence latencies in the N1 ($F(2,21) = 1.524; p = .241$) and P3 ($F(2,21) = .612, p = .552$) segment.

### 3.5. N1 and P3 amplitude

No significant differences were observed with regard to amplitudes in the N1 segment. In the P3 segment at maxi-

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**Table 3**

Amplitude and latency in the N1 and P3 segment of the study patients

<table>
<thead>
<tr>
<th></th>
<th>FEC group (N = 17)</th>
<th>CTC group (N = 12)</th>
<th>CMF group (N = 24)</th>
<th>Control group (N = 23)</th>
<th>All chemotherapy (N = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 latency</td>
<td>100 (7)</td>
<td>106 (9)</td>
<td>100 (11)</td>
<td>101 (13)</td>
<td>101 (10)</td>
</tr>
<tr>
<td>N1 amplitude</td>
<td>9.2 (3.6)</td>
<td>8.9 (2.2)</td>
<td>8.9 (2.5)</td>
<td>8.7 (2.6)</td>
<td>9.0 (2.8)</td>
</tr>
<tr>
<td>P3 latency</td>
<td>325 (51)</td>
<td>341 (51)$^a$</td>
<td>301 (42)$^a$,</td>
<td>329 (53)</td>
<td>318 (49)</td>
</tr>
<tr>
<td>P3 amplitude</td>
<td>11.5 (3.6)$^{b,c}$</td>
<td>12.1 (3.0)</td>
<td>13.4 (3.9)</td>
<td>14.5 (3.4)$^{b,c}$</td>
<td>12.5 (3.7)$^c$</td>
</tr>
</tbody>
</table>

Latency in milliseconds, amplitude in microvolt. All values expressed as mean (SD). All chemotherapy: all patients treated with chemotherapy (FEC, CTC and CMF) combined.

- $^a$ CTC group versus CMF group $p = .023$.
- $^b$ FEC group versus control group $p = .011$.
- $^c$ All chemotherapy versus control group $p = .030$.
mal GFP, however, ANOVA revealed a borderline significant difference between the treatment groups in total amplitude ($F(3, 72) = 2.646; p = .055$, see Table 3 for group means).

In patients treated with FEC chemotherapy smaller P3 amplitudes were observed compared to the control group. Between-group comparisons showed a mean difference of 3.0 μV between the FEC patients and the controls with a $p$-value of .011. Patients treated with high-dose CTC chemotherapy had a lower mean total amplitude (2.4 μV) than the controls, but this difference did not reach significance ($p = .068$). $t$-Tests showed a significant difference in total P3 amplitude between patients treated with chemotherapy and patients not treated with chemotherapy ($t(2,74) = -2.216; p = .030$). Within the CMF group, tamoxifen use did not significantly influence N1 ($F(2,21) = .331; p = .722$) and P3 ($F(2,21) = .035; p = .966$) amplitude.

### 3.6. Localization of maxima

No significant differences were revealed by ANOVA with regard to x- and y-co-ordinates of the N1 and P3 component. Also, patients treated with chemotherapy, independent of treatment regimen, did not differ in co-ordinates of the N1 and P3 from patients not treated with chemotherapy. However, between-group comparisons showed that with regard to the x- and y-co-ordinates of the N1 component, CMF patients differed from CTC patients in the x-co-ordinate, with a lower mean value for the x-co-ordinate in the CMF patients ($t = -2.374; p = .020$, their maximum negative value (trough) appears at a more left-sided localization compared to the CTC patients, see Fig. 2). Their y-co-ordinate differed from the FEC patients in that their maximum negative value had a more posterior localization.

In addition, differences between treatment groups were also observed in the x-co-ordinates of the P3 component as well for the trough (maximum negative value) as the peak (maximum positive value, see Fig. 2). The maximum negative value in the P3 segment of CMF patients differed from the maximum negative value of FEC patients ($t = -2.424; p = .018$, it occurred at a more left-sided localization). With regard to the maximum positive value, the patients in the CTC group differed from patients in the CMF group with a localization more on the right-side of the midline ($t = -2.437; p = .017$).

Independent samples $t$-test did not reveal differences in co-ordinates of the P3 between all patients treated with chemotherapy (independent of treatment) and patients not treated with chemotherapy.

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![Fig. 2. N1 and P3 topography as described by positive and negative maxima of the global field power. Significant differences at a $p$-value of <.0238: N1 maximum negative value: CMF versus CTC ($p = .020$); P3 maximum negative value: CMF versus FEC ($p = .018$); P3 maximum positive value: CMF versus CTC ($p = .017$).]
4. Discussion

As part of a research line studying the effects of chemotherapy on cognitive functioning, we examined the effects of various regimens of adjuvant chemotherapy on ERP amplitude and latency in breast cancer survivors using an auditory oddball task. We did not find any differences in N1 amplitude or latency between the chemotherapy groups and the control group. As there was no delay in this primary component, early perceptual processes appeared to be intact in these patients treated with chemotherapy. With regard to the P3 component, we observed the lowest P3 amplitude in patients treated with FEC chemotherapy, followed by the CTC and the CMF group. Overall, significantly lower P3 amplitudes were measured in patients treated with chemotherapy compared to patients not treated with chemotherapy. These lower amplitudes indicate that there are fewer neurons that fired synchronously in patients treated with chemotherapy at the moment of the P3. A difference in P3 latency between the CMF group and the CTC group was found, with the CMF group showing a shorter latency. We also found differences between the treatment groups in the co-ordinates of the peaks and troughs. For the N1 component, the maximum negative value appeared to have shifted to the left-side compared to the other three groups. For the P3 component, the localization of the maximum negative value in the CMF patients had also shifted to the left-side compared to the FEC group. The maximum positive value of the CTC group appeared to have shifted to the right compared to the CMF group. So, there appeared to be some small differences in the structure of the potential field between the groups.

Decreased P3 amplitudes are associated with normal aging (Kok, 2000) and may thus reflect damage of cytotatic agents that results in accelerated aging processes in the brain. Decreased P3 amplitudes are also associated with various psychopathologies and have been observed in ADHD, dementia and schizophrenia (Saito et al., 2001; Barry et al., 2003; Van der Stelt et al., 2004). The decreased amplitude of the P3 in patients treated with chemotherapy might indicate that cytostatic agents bring about damage to the central nervous system. Therefore, this effect might have been caused by cytostatic agents that all regimens have in common. All patients were treated with cyclophosphamide and 5-fluorouracil and these agents might be possible candidates for the effect on P3 amplitude.

As all patients in the FEC and CTC groups and 50% of the CMF group were past or current tamoxifen users, tamoxifen might also be associated with the observed changes in P3 amplitude. We performed an additional analysis within the CMF group and compared current, past and never users of tamoxifen. We did not find any significant differences between current, past and never users of tamoxifen on any of the outcome measures, but the numbers of the three subgroups were very small, and the potential, biologically plausible, contribution of tamoxifen needs further investigation.

In line with the results of a previous study we measured a relatively short P3 latency in the CMF group (Kreukels et al., 2005). This was surprising because P3 latency is generally prolonged in disorders with cognitive dysfunction (for instance, schizophrenia and dementia, Pfefferbaum et al., 1995a). There are, however, some disorders associated with cognitive deficits in which reduced P3 latencies have also been observed, such as ADHD and obsessive-compulsive disorder (OCD, Oades et al., 1996; Moraut et al., 1997). It has been suggested that the shorter latencies in these patients could be the result of a speeding of cognitive processing. Difficulties in inhibitory mechanisms might play a role in this speeding of processing, as is also speculated in the OCD-litterature. The speeding of P3-related processing may not improve task performance, as was also seen in our previous study (Kreukels et al., 2005): reaction times appeared to be somewhat longer in CMF patients compared to the control group. A possible explanation for this pattern of results is in terms of rushed stimulus-evaluation and subsequent compensation. The quality and extent of stimulus-evaluation processes may have been insufficient to extract fully adequate information from the stimuli, yielding preliminary outputs which in turn may have required more elaborate processing in response-related stages to compensate for the superficial levels of stimulus evaluation.

Diminished P3 latencies were also reported following administration of yohimbine and d-amphetamine (Halliday et al., 1994). In addition, these drugs were associated with a speeding of the N1 component as well. To investigate if the reduced P3 latency in the CMF group is preceded by earlier ERP components with reduced latency, we examined the N1 component. We did however not observe any differences in N1 amplitude or latency between the CMF group and the other groups. Therefore, the earlier P3 does not appear to be associated with a decrease in duration of early sensory processing.

There was, however, a difference in the co-ordinates of the trough of the N1 in the CMF group compared to the CTC group. We found a relative shift of the maximum negative value to the left of the CMF group compared to the CTC group (and non-significantly compared to the other groups). A possible explanation for the shift in the potential field in CMF patients might be a general dysfunction in neurons during the N1, which resulted in a slight shift to the dominant hemisphere where most neurons are located that deal with auditory processing (left hemisphere). This general dysfunction is, however, not reflected in changes in N1 amplitude and latency in these patients.

The P3 latency in the CTC group was prolonged compared to the CMF group, which is more in line with the finding that P3 is generally prolonged in various disorders associated with cognitive deficits (Pfefferbaum et al., 1995a). Heukrodt et al. (1988) also found a significantly prolonged P3 latency in long-term acute lymphoblastic leukemia survivors as well as in patients successfully treated with chemotherapy for solid tumors. In addition, we
observed a slight difference in the structure of the potential field during the P3 between the CTC group and the CMF and control group (although the difference between CTC and control group did not reach significance), that might indicate that the activity measured on the scalp reflects a shift in potential field as a result of dysfunction in neurons in the CTC group.

The effects of adjuvant chemotherapy regimens on P3 latency appear to be more specific than their effects on P3 amplitude. The P3 latency in the CMF group was relatively short, whereas it was somewhat prolonged in the CTC group. This might indicate that these specific effects are related to specific agents in the different chemotherapy regimens. Possibly, decreased latency in CMF patients was caused by an effect of one of the agents in the CMF regimen that resulted in the speeding of processing. This decrease in latency was not observed in the patients treated with FEC chemotherapy. The CMF regimen differs from the FEC regimen in that epirubicin is replaced by methotrexate (MTX). Therefore, MTX might be associated with the observed decrease in P3 latency in the CMF group.

Neurotoxicity is reported as a complication of intrathecal methotrexate administration either alone or in combination with cranial irradiation and of high-dose intravenous methotrexate given as single treatment (Boogerd, 1995). Dosages of methotrexate in the CMF regimen are, however, much lower and not known to penetrate the blood-brain barrier (Bleyer, 1981).

To distinguish between the different treatment regimens, all groups were compared with each other and not only with the control group. These comparisons have an exploratory character and these differences can help us in identifying and understanding specific differences in brain dysfunction between the groups. The results can help us in generating hypotheses for future research in which these differences between the groups can be studied in more detail.

With the results of the present study we could distinguish between a more general effect of chemotherapy on P3 amplitude and a more specific effect of different regimens on P3 latency. When studying P3 latency in heterogeneous treatment groups, the opposite effects on P3 latency by different regimens might lead to the erroneous conclusion that there is no effect of the regimens under study on P3 latency. In heterogeneous treatment groups, it might be more sensible to study the effects on P3 amplitude.

The results of the current study together with those of previous neurophysiological studies indicate different patterns of EEG and ERP abnormalities in patients treated with different regimens of chemotherapy. There is an urgent need for research that can reveal the mechanisms underlying the cognitive deficits and the EEG and ERP abnormalities in patients treated with adjuvant chemotherapy (Ahles and Saykin, 2007). Animal studies that could probably help us in determining the specific agents or combination of agents that cause these effects are now beginning to surface (Lee et al., 2006; Reiriz et al., 2006; Winocur et al., 2006; Macleod et al., 2007; Seigers et al., 2008).

In addition, a combination of imaging techniques like MRI and PET with neuropsychological tests could help us to unravel the mechanisms underlying cognitive deficits following chemotherapy. Few studies have been published that used other imaging techniques to search for functional and structural changes in the brain in patients treated with adjuvant chemotherapy. A study by Inagaki et al. (2007) examined adverse effects of adjuvant chemotherapy on white and grey matter volume in breast cancer survivors. They found significant reductions in white and grey matter volume and significant correlations of these reductions with memory function in breast cancer survivors treated with adjuvant chemotherapy. Silverman and colleagues acquired PET scans and found that during performance of a short-term recall task, cerebral blood flow in regions of frontal cortex was significantly larger in breast cancer survivors who had received adjuvant chemotherapy 5–10 years before, relative to controls (Silverman et al., 2007). Comparable findings were reported in a twin study in which one of the twins contracted breast cancer and received chemotherapy, whereas the other did not (Ferguson et al., 2007).

Future studies should focus on distinct treatment regimens in the analysis of their effects on brain functioning. It may very well be that each chemotherapy regimen has its own cognitive toxicity profile. Parallel neuropsychological, neuroimaging and psychosocial assessments in large homogeneous groups are necessary to define such profiles associated with specific chemotherapeutic regimens and their late neurocognitive complications. Every piece of evidence for abnormalities in brain and neurocognitive functioning following cytostatic treatment might help us in solving the puzzle of the underlying mechanisms.

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