Patients with Persistent Pain after Breast Cancer Treatment Show Enhanced Alpha Activity in Spontaneous EEG

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Abstract

Objective. The aim of the present study was to investigate whether patients with persistent pain after breast cancer treatment show an enhanced and slowed dominant alpha activity in their electroencephalogram (EEG) recorded during rest in comparison with patients that also had undergone breast cancer treatment but do not have pain.

Methods. The spontaneous EEG was recorded during rest and before painful stimulation of the calf and analyzed with spectral analysis (Fast Fourier Transformation). Outcome measures, i.e., alpha indices (center of gravity and overall amplitude), were statistically tested between patients with and without persistent pain.

Results. In comparison with patients without pain, patients with persistent pain after breast cancer treatment show more alpha activity in their spontaneous EEG observed from parietal-occipital brain regions.

Conclusion. Persistent pain after breast cancer treatment affects spontaneous brain activity, which might influence cognitive functioning.

Key Words. Breast Cancer Treatment; Persistent Pain; Electroencephalogram; Resting State; Alpha

Introduction

The awake human electroencephalogram (EEG) recorded during rest is typically dominated by activity in the 7–13 Hz (i.e., alpha) frequency range. This dominant alpha activity is most prominent over parietal and occipital cortices, and is largest when the eyes are closed [1–4].

Sarnthein et al. [3] showed that this dominant alpha activity, recorded during rest, is enhanced and slowed in predominantly patients with peripheral neurogenic pain. The same authors also demonstrated that pain treatment (i.e., therapeutic lesion of the central lateral thalamus) not only results in a gradual or immediate pain decrease, but also in normalization of the alpha activity [3].

More recently, Olesen et al. [5] also showed enhanced alpha activity in the EEG recorded during rest in patients with chronic pancreatitis pain, which is hypothesized to be, at least partly, of peripheral neurogenic origin [6,7].

The above studies suggest a relationship between peripheral neurogenic pain and alterations in the spontaneous EEG. However, in these studies, matched healthy volunteers were used as a control group, which makes it difficult to ascribe the observed effects solely to the pain as it is also possible that they are the consequence of the underlying pathophysiology, for example, the presence of neuropathy per se. To overcome this problem, a control patient group with the same underlying pathophysiology but with no pain should be included for comparison.

Twenty-five to sixty percent of the women who receive breast cancer treatment (including mastectomy (MAST) or lumpectomy (LUMP), axillary lymph node dissection (ALND), chemotherapy, radiation therapy, and hormone therapy) suffer from persistent pain that is, at least partly, of peripheral neurogenic origin [8,9]. The aim of the present study was to test the hypothesis if patients with...
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persistent pain after breast cancer treatment show an enhanced and slowed dominant alpha activity in their spontaneous EEG in comparison to patients that also had undergone breast cancer treatment but do not have pain.

Materials and Methods

Ethics Statement

Approval for the study was obtained from the medical and ethical review board, Committee Region Arnhem-Nijmegen, Nijmegen, The Netherlands (NL.30189.091.09). All patients signed an informed consent form.

Patients

This article is based on the dataset of a patient group whose primary analysis (event-related potentials) has already been reported [10]. The present work presents an analysis of the spontaneous EEG. The study comprised 19 patients (8 women with persistent pain and 11 without pain) who were treated for breast cancer. Data about the type of pain and pain-related sensory signs in the patients with pain were collected using the Douleur Neuropathique 4 (DN4) questionnaire [11,12]. For details on the patients’ demographical and clinical characteristics, see van den Broeke et al. [10]. In short, patients with pain were included if they considered themselves to have pain as a result of the breast cancer treatment, persisting continuously or intermittently for more than 3 months after surgery (yes or no) [13]. All patients (with and without pain) had been operated ≥ 1 year ago at the time of participating. All patients had undergone a MAST or LUMP and ALND. Only patients who had unilateral breast cancer were included. Patients were excluded from the study if they:

1. underwent breast reconstruction,
2. had a psychiatric or neurological condition (neurological signs as a result of the anticancer treatment excepted),
3. used pain medication or other medication that potentially affects brain processing like antidepressants, antipsychotics, anticonvulsants, and benzodiazepines (hormone therapy excepted), and
4. suffered from any preexisting pain or pain syndrome.

EEG Recordings

A multichannel EEG (BrainVision, Brain Products GmbH, Waldkirch, Germany) was recorded during the experiment (band-pass 0.1–100 Hz, sampling frequency 2,000 Hz), with 64 active electrodes. The electrodes were arranged according to the international 10–20 system, and electrode CPz was used as reference. Eye movements were detected by horizontal and vertical electro-oculogram (EOG) recordings. Horizontal EOG was measured from the outer canthus of the left eye and vertical EOG supraborital to the left eye. Impedance was kept under 20 kΩ for all leads.

Procedure

Spontaneous EEG was recorded in two conditions: during rest (EEG recorded for 1 minute) and before painful stimulation (i.e., prestimulus; the EEG recorded before each painful stimulus). During painful stimulation, patients received passively 20 painful electrical stimuli on the calf with a random interstimulus interval between 8 and 10 seconds (for more details see van den Broeke et al. [10]). The analysis of the poststimulus pain-evoked responses are already published (see van den Broeke et al. [10]) The prestimulus condition was included for analysis in order to determine the consistency of alpha activity within one patient. Both measurements (EEG during rest and prestimulus) took place on the same day whereby the measurement of the rest EEG always preceded the measurement of the prestimulus EEG. In both conditions, patients were instructed to sit as still as possible, with eyes closed and without making any movements.

Signal Analysis

The software Brain Vision Analyzer v. 1.05 (Brain Products GmbH) was used for offline EEG signal analysis.

As preprocessing steps the continuous EEG was downsampled to 500 Hz and band pass filtered (Butterworth zero phase) between 1 and 30 Hz. After that, the EEG was segmented into epochs of 4 seconds. For the continuous EEG recorded before painful stimulation (i.e., prestimulus EEG), this means that before every stimulus onset, a window of 4 seconds EEG was collected. Bad segments containing ocular artifacts were corrected using the Gratton–Coles method [14]. Segments were also inspected for other artifacts like muscle or jaw and line noise activity and were removed if necessary. None of the epochs were rejected because of artifacts. A Fast Fourier Transformation (FFT) was applied to each single epoch of each patient. For the FFT, a Hanning window was used with a resolution of 0.1 Hz. Then, for each electrode separately, the FFTs were averaged across epochs.

Because it has been shown consistently that the EEG recorded during rest is typically dominated by alpha activity maximal at the parietal-occipital cortices [1–4], we clustered the FFT spectra of the posterior electrodes: Oz, O1, O2, P1, P2, P3, P4, P0z, P5, P6, P7, and P8, and used the averaged spectrum of this region of interest (ROI) for subsequent analysis. From this ROI, the overall alpha amplitude [4] as well as the center of gravity (CoG) [4,15,16] were calculated. The CoG value is the frequency at which the amplitude within the empirically defined window is split into two equal parts, and thus each part has the same overall amplitude [4]. We opted for these two parameters, instead of the alpha peak amplitude and peak frequency [3,4], because it has been shown that the CoG is a more stable parameter than peak frequency [16]. Besides, not all individuals show one clear dominant peak in their FFT spectrum, which is problematic in determining the dominant peak amplitude [4], so in anticipation to that, we calculate the overall amplitude.
In line with the study of Schmidt et al., we first empirically determine the alpha window [4]. To this end, we calculated the mean peak frequency (i.e., frequency corresponding to the highest absolute amplitude value within the arbitrary 7–13 Hz alpha window) across all patients as well as the lower and upper limits, defined by ± two standard deviations [4]. Subsequently, the overall amplitude and CoG were calculated for each patient within the empirically defined alpha window. The overall amplitude was computed as the sum of values within the empirically defined window. The CoG was calculated by the following equation [15]:

$$\text{CoG} = \frac{\sum (a_i \times f)}{\sum a_i}$$

where,

$a_i =$ amplitude of frequency $f$

$f =$ frequencies within the empirically defined alpha window

Statistical Analysis

For statistical analysis, the software SPSS v. 16.0 (SPSS Inc., Chicago, IL, USA) was used.

Because of the small sample size and non-Gaussian distribution of the data, nonparametric test statistics were used. Differences in overall amplitude and CoG between the two groups were statistically tested with the Mann–Whitney U-test statistic. Correlations were calculated according to Spearman ($r$). The effect size ($r$), a measure of the strength of the relationship between two variables, was calculated for between-group differences. The effect size $r$ was calculated as the $Z$-score divided by the square root of the total number of observations. For all tests, the level of statistical significance was set at $P < 0.05$.

Results

Clinical and Demographic Characteristics

Patients characteristics are shown in Table 1.

No statistically significant differences were observed between the two groups with respect to age, menopausal status, and arm volume differences (Table 1). No significant associations were observed between the two patient groups regarding the type of surgical intervention (mastectomy + axillary lymph node dissection or lumpectomy + axillary lymph node dissection) and incidences of adjuvant therapies (chemotherapy, radiation therapy, or hormone therapy; Table 1).

Electrophysiological Measurements

Mean Alpha Peak Frequency and Its Lower and Upper Limits

Mean peak frequency of EEG in rest ($N = 19$) was 9.6 Hz (lower and upper limits were 7.9 and 11.2 Hz). Mean peak frequency of prestimulus EEG ($N = 19$) was 9.8 Hz (lower and upper limits were 8.4 and 11.3 Hz).

Correlation Between Rest and Prestimulus Alpha Indices

Significant strong positive correlations ($N = 19$) were observed between rest and prestimulus alpha indices (CoG and overall amplitude). Correlation between rest and prestimulus CoG was $r = 0.94$, $P < 0.001$ (two sided), and between rest and prestimulus overall amplitude $r = 0.94$, $P < 0.001$ (two sided).

EEG in Rest

The median (7.9–11.2 Hz) overall alpha amplitude was significantly larger in patients with pain compared to patients without pain ($U = 23.0$, $P = 0.045$ [one sided], $r = -0.40$). Median (and interquartile ranges) overall amplitude were: patients with pain 10.90 (8.34–16.55) mV, patients without pain 7.15 (3.48–12.54) mV (Figure 1). The alpha frequency (CoG) observed in the patients with pain was not statistically significantly lower than the alpha frequency (CoG) of the patients without pain (Figure 1).

Prestimulus EEG

The median (8.4–11.3 Hz) overall alpha amplitude was significantly larger in the patients with pain compared to patients without pain ($U = 21.0$, $P = 0.032$ [one sided], $r = -0.44$). Median (and interquartile ranges) overall amplitude were: patients with pain 11.29 (8.36–16.18) mV, patients without pain 6.65 (3.55–12.19) mV (Figure 1). The alpha frequency (CoG) observed in the patients with pain was not statistically significantly lower than the alpha frequency (CoG) of the patients without pain (Figure 1).

Correlation Between Reported Pain Intensity and Alpha Indices

No statistically significant correlations were observed between the reported pain intensity at the day of measurement or averaged over the past 3 months and the overall alpha amplitude, or between the reported pain intensity and frequency (CoG).

Discussion

This study shows that patients with persistent pain after breast cancer treatment show more alpha activity in their spontaneous EEG than patients that also had undergone breast cancer treatment but do not have pain.

Spontaneous Brain Activity and Peripheral Neurogenic Pain

The observed enhanced alpha activity in the patients with pain is in agreement with the studies of Sarnthein et al. [3] and Olesen et al. [5], and suggests a relationship with the presence of peripheral neurogenic pain. However, it seems unlikely that alpha activity is directly related to the...
Table 1 Demographic and clinical characteristics of the patients: (a) with pain and (b) without pain

(a)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (Years)</th>
<th>Menopausal Status</th>
<th>Surgical Treatment</th>
<th>Additional Treatment</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>Post</td>
<td>MAST + ALND (II)</td>
<td>Yes (FEC) Yes (TAM)</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>Post</td>
<td>MAST + ALND (II)</td>
<td>Yes (TAC) No</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>Post</td>
<td>MAST + ALND (II)</td>
<td>Yes (TAC) Yes (TAM)</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>Post</td>
<td>MAST + ALND (II)</td>
<td>Yes (TAC) Yes (TAM)</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>Post</td>
<td>MAST + ALND (II)</td>
<td>Yes (FEC) Yes (TAM)</td>
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<tr>
<td>6</td>
<td>49</td>
<td>Post</td>
<td>LUMP + ALND (II)</td>
<td>Yes (FEC) Yes (TAM)</td>
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<tr>
<td>7</td>
<td>65</td>
<td>Post</td>
<td>MAST + ALND (II)</td>
<td>Yes (TAC) Yes (TAM)</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>Post</td>
<td>MAST + ALND (II)</td>
<td>No</td>
</tr>
<tr>
<td>Median</td>
<td>52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–Q range (%)</td>
<td>49–61</td>
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</table>

Median 52
I–Q range 49–61

(b)

<table>
<thead>
<tr>
<th>Arm Volume Difference (mL)</th>
<th>Location of Pain</th>
<th>Intensity Pain (NRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Affected Side—Unaffected Side</td>
<td>Mean Score of Last 3 Months</td>
</tr>
<tr>
<td>1 200</td>
<td>Arm + chest</td>
<td>6</td>
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<tr>
<td>2 −50</td>
<td>Arm</td>
<td>6</td>
</tr>
<tr>
<td>3 −60</td>
<td>Small area arm + chest (nipple and armpit)</td>
<td>6</td>
</tr>
<tr>
<td>4 20</td>
<td>chest</td>
<td>3</td>
</tr>
<tr>
<td>5 170</td>
<td>Upper arm + chest</td>
<td>6</td>
</tr>
<tr>
<td>6 −40</td>
<td>arm</td>
<td>3</td>
</tr>
<tr>
<td>7 60</td>
<td>Small area arm + chest</td>
<td>4</td>
</tr>
<tr>
<td>8 −110</td>
<td>Armpit (upper arm + top) + chest (scar)</td>
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</tr>
<tr>
<td>Median</td>
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<td></td>
</tr>
<tr>
<td>I–Q range (%)</td>
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<td></td>
</tr>
<tr>
<td>Patient</td>
<td>Age (Years)</td>
<td>Menopausal Status</td>
</tr>
<tr>
<td>---------</td>
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</tr>
<tr>
<td>1</td>
<td>32</td>
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<tr>
<td>2</td>
<td>49</td>
<td>Post</td>
</tr>
<tr>
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<td>58</td>
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</tr>
<tr>
<td>4</td>
<td>45</td>
<td>Post</td>
</tr>
<tr>
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<td>8</td>
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<td>Post</td>
</tr>
<tr>
<td>9</td>
<td>47</td>
<td>Post</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>Post</td>
</tr>
<tr>
<td>11</td>
<td>68</td>
<td>Post</td>
</tr>
<tr>
<td>Median</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>I–Q range (%)</td>
<td>45–58</td>
<td></td>
</tr>
</tbody>
</table>

ALND = axillary lymph node dissection with between brackets the level of axillary dissection I, II, or III; ARI = Arimidex (AstraZeneca, London, UK); FEC = fluorouracil + epirubicin + cyclophosphamide; LUMP = lumpectomy; MAST = mastectomy; NRS = numerical rating scale; TAC = docetaxel (Taxotere, Sanofi, Paris, France) + doxorubicin (Adriamycin, Pfizer, New York, NY, USA) + cyclophosphamide; TAM = Tamoxifen.
pain experience because we did not observe correlations between alpha amplitude and the pain scores obtained at the day of measurement. Also Olesen et al. did not observe a significant correlation between the reported pain intensity and alpha power in their patients with pain. In the study of Sarnthein et al., alpha power was clearly enhanced in the patients with pain, but no correlations between alpha power and pain intensity are mentioned.

Recently it has been observed that the spontaneous alpha power observed from the parietal-occipital is modulated by the intensity of throbbing sensation [17]. But the coherence between the throbbing pulsations and alpha power was weaker when the throbbing sensation had a low intensity. If this is also the case in our patients, this might have contributed to the lack of correlation between pain intensity and alpha power as most patients rated their pain intensity at the day of measurement with a numerical rating scale score of 1. Moreover, Schmidt et al. [4] did observe significant correlations between reported pain intensity and alpha power in patients with chronic low back pain; the higher the pain ratings, the larger the alpha power. However, these correlations were stronger for the pain intensity averaged over the last 4 weeks to 12 months but were weaker and mostly not significant for the pain intensity observed at the day of measurement. Based on their findings, the authors speculated that alpha power probably resembles a process associated with pain chronification but not the pain experience itself [4]. In our study, we did not observe a significant correlation between the reported pain intensity averaged over the last 3 months and the alpha amplitude. Thus, at present, it is still unclear how enhanced alpha is related to persistent pain.

In contrast to the study of Sarnthein et al., we did not observe a slowing of the dominant alpha frequency in the patients with pain. At least two hypotheses could be put forward to explain this. First, the average pain duration of the patients in the study of Sarnthein et al. [3] was longer. Second, the slowing of alpha could be unspecific for pain but more related to other psychological variables. This hypothesis seems to be supported by the study of Schmidt et al. [4] who observed significant correlations between psychological variables and alpha frequency in their patients with pain. The lower the alpha peak frequency, the larger the psychopathology or the lower life satisfaction was. No correlations were observed between psychological variables and alpha power or pain intensity [4]. Moreover, alpha slowing is also observed in patients with burnout [18]; this finding supports the hypothesis that alpha slowing is unspecific for pain.

An important methodological limitation of this study is the small sample size, and therefore the results regarding alpha activity could be due to chance. However, a moderate effect size is observed that seems to support the relevance of our findings. Moreover, the fact that the enhanced alpha activity in the patients with pain is observed in separate measurements shows that it is consistent over time. Nevertheless, further studies with larger sample sizes are necessary to confirm the results of the present article.
Conclusion

The awake human EEG recorded during rest (eyes closed) is typically dominated by alpha activity (7–13 Hz), which is maximal over parietal and occipital cortices. The present study shows that this alpha activity is enhanced in patients with persistent pain after breast cancer treatment. It is yet unclear what the role of this enhanced posterior alpha activity is in relation to the patients’ pain.

References


