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ORIGINAL INVESTIGATION

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Acute and subchronic effects of amitriptyline on processing capacity in neuropathic pain patients using visual event-related potentials: preliminary findings

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Abstract *Rationale:* Little is known about the effects of low doses of amitriptyline, prescribed in the treatment of neuropathic pain, on attentional processing capacity. *Objectives:* Changes due to amitriptyline treatment on attentional processing capacity were investigated on behavioral measures and event-related brain potentials (ERPs) in six patients with neuropathic pain. *Materials and methods:* Patients were treated for 15 consecutive days with 25 mg nocturnally administered amitriptyline or placebo in a double-blind crossover randomized design. Measurements were carried out on day 1 and day 15 of each treatment period. An attentional capacity probe task was used in which the difficulty level was manipulated, resulting in an easy and a hard condition, while task-irrelevant visual probes were presented. During task performance, ERPs were measured from the midline electrodes Fz, Cz, Pz, and Oz. *Results:* Amitriptyline increased reaction times (RTs) after acute but not after subchronic administration. ERP analyses showed that P3 amplitudes to the task stimuli were not affected by amitriptyline in either treatment phase. Moreover, P3 amplitudes to the probes were increased in the easy compared to the hard task condition after subchronic amitriptyline treatment, indicating beneficial effects of repeated amitriptyline administration. In contrast, acute amitriptyline administration did reduce an earlier visual evoked potential, N1, preceding the P3 component. *Conclusions:* The results suggest that amitriptyline, even at low dosages of 25 mg, affects performance after acute administration in chronic neuropathic pain patients. After 2 weeks of treatment, performance appears to be unaffected. No deficits in processing capacity due to amitriptyline treatment were found.

Keywords Amitriptyline · Neuropathic pain · ERPs · Processing capacity · Attention

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Introduction

The efficacy of amitriptyline in the treatment of chronic neuropathic pain caused by lesions in the peripheral or central nervous system has consistently been demonstrated (McQuay et al. 1996). Hence, amitriptyline is frequently prescribed as an analgesic drug. However, besides alleviating pain, amitriptyline has a known severe side-effect profile due to anticholinergic and antihistaminergic actions and α_1-adrenoceptor blocking, which may cause sedation and performance deficits on a wide variety of tasks (see Deptula and Pomara 1990; Thompson 1991; Knegtering et al. 1994; Amado-Boccara et al. 1995; Volz and Sturm 1995 for reviews). Obviously, the main objective of pharmacological treatment is to allow the patient to regain active life and work; therefore, the degree of side effects should be tolerable and should not interfere with daily activities. Two precautions have been made in administrating amitriptyline to avoid the occurrence of side effects as much as possible. First, the drug is most often prescribed for bedtime administration. In this way, the sedative side effects may even have a favorable effect since many pain patients have sleep problems. Second, low dosages of amitriptyline are prescribed. Even at low dosages of 10 or 25 mg, amitriptyline

appears to have analgesic properties in contrast to higher dosages necessary to treat depression, which typically start at 75 mg daily. Although a huge amount of research has found that amitriptyline in an antidepressant dose deteriorates cognitive performance in healthy controls and depressive patients, the results of these studies may not necessarily apply to patients with chronic pain since amitriptyline is administered nocturnally in low dosages in the treatment of pain.

Several studies have demonstrated that chronic pain patients, irrespective of pharmacological treatment, have difficulties in performing tasks that place high demands on attentional resources (e.g., Eccleston 1994; Dick et al. 2003), although some reports failed to find such effects (Houlihan et al. 2004). Thus, pain itself may have detrimental effects on cognitive performance. Hence, the therapeutic pain-relieving effects of amitriptyline may enhance cognitive abilities. Therefore, it might be possible that the performance of pain patients on cognitive tasks is improved with amitriptyline treatment compared to without amitriptyline treatment.

Event-related potentials (ERPs) are commonly used as a measure of processing capacity. Specifically, one of the endogenous ERP components, the P3, is thought to reflect attentional processing demands that are employed to a task (Polich and Kok 1995). P3 amplitude is a reflection of electrical brain activity originating from multiple neural sources (Bledowski et al. 2004). A commonly used task in the study of attentional resource demands is the probe task (Kenemans et al. 1992; Verbaten et al. 1997; Jonkman et al. 2000; Hoeksma et al. 2004). In the probe task, secondary task-irrelevant probes are presented against a background of a continuous ongoing primary task of which the difficulty level is manipulated. These task-irrelevant probes are expected to provide the most pure estimate of processing capacity since they are relatively free from target-related processes (Kramer et al. 1995). It has been demonstrated that when the difficulty level of the primary task increases, P3 amplitude to task-relevant stimuli increases, reflecting that more attentional resources are invested in the harder task (Wickens et al. 1983). P3 amplitude elicited by task-irrelevant probes is thought to reflect a trade off in processing demands. When demands of the primary task increase, the P3 amplitude to these task-irrelevant probes decreases, probably reflecting lower spare resources to invest in the secondary task (Wickens et al. 1983).

Little is known about the acute and subchronic effects of amitriptyline on attentional processing capacity tasks. On the one hand, given the sedative potential of amitriptyline, performance on a task requiring high attentional investment may be impaired since side effects can be expected to emerge shortly after first administration, while the therapeutic pain-relieving effects may be delayed. On the other hand, attentional processing task performance might actually improve since tolerance develops for the sedative side effects after repeated dosing of amitriptyline and also because of the therapeutic efficacy of amitriptyline in relieving pain. Indeed, several studies found that, in general, tolerance develops to the sedative side effects after repeated administration of amitriptyline within 1–2 weeks on subjective and behavioral measures (e.g., Deptula and Pomara 1990; Robbe and O'Halon 1995). However, van Laar et al. (2002) also demonstrated that 75 mg of amitriptyline (50 mg administered at evening and 25 at morning) may reduce P3 amplitude in attentional tasks even after 1 week of treatment, suggesting that tolerance may develop at different paces for different measures.

The present study was designed to study the effects of 25 mg nocturnally administered amitriptyline on attentional processing capacity in neuropathic pain patients. The effects of 25 mg amitriptyline were compared to placebo after single (day 1, acute effects) and repeated (day 15, subchronic effects) administration. This regimen allowed us to examine both the acute effects and possible tolerance development. The probe task was used to investigate attentional processing capacity, and ERP P3 amplitudes were measured. Furthermore, exploratively, ERP waves preceding the P3 component were also examined for drug effects.

The effects of amitriptyline on attentional processing capacity were mainly expected after acute administration since side effects generally occur shortly after first administration, while therapeutic pain-relieving efficacy of amitriptyline may be delayed. In detail, regarding the task-relevant stimuli, it was expected that amitriptyline would reduce P3 amplitude. With regard to the more sensitive measure of attentional resources, the task-irrelevant probe stimuli, it was hypothesized that after acute administration of amitriptyline, P3 amplitudes to the probe stimuli would be reduced more in the amitriptyline drug condition compared to placebo, and P3 amplitudes would be reduced more in the hard task compared to the easy task condition, i.e., an interaction between task and drug was expected. Further, it was assumed that after subchronic treatment of amitriptyline, the impairing effects would be diminished due to the development of tolerance to the side effects. That is, comparable P3 amplitudes to the probes and task stimuli were expected after amitriptyline and placebo, or even a small improvement after amitriptyline, i.e., higher P3 amplitude, since pain will be reduced under amitriptyline compared to placebo.

Materials and methods

Subjects

Twelve patients with neuropathic pain participated in the study. Three patients withdrew after the training session, one because of pain rebound and two because of employment obligations that conflicted with study participation. Two patients used psychoactive medication during the study and were excluded from the data analysis. Further, data of one patient were lost due to procedural difficulties. The remainder of six patients with neuropathic pain were included in the data analysis.

Participants were recruited from October 2002 to December 2004 by seven pain clinics in Utrecht and surrounding areas in the Netherlands, coordinated by the University

Medical Center Utrecht. Patients were included if they had benign pain of moderate to severe intensity (at least 4 cm on a 10-cm scale) for at least 3 months, measured with a visual analog scale (VAS) by the pain physician. Patients had to be responders to amitriptyline; in other words, amitriptyline medication had to be effective in pain relief, since our particular interest was to study this medicine when used as an effective therapy. Patients all used amitriptyline prior to study participation for at least 5 months. Further, patients were right handed and had normal or corrected-to-normal vision.

Patients were excluded from the study if they used other psychotropic medication than the study medication, suffered from an alcohol or drug dependence, psychological or psychiatric disorders, or severe physical disorders. Heavy smokers and caffeine users were also excluded. The use of paracetamol and/or nonsteroidal anti-inflammatory drugs (NSAIDs) was allowed as escape medication. All other (il)licit drugs, apart from oral contraceptives, were prohibited during the total study period. On each test day, compliance was tested using a urine drug screening [amphetamines, barbiturates, benzodiazepines, cocaine, morphine, and tetrahydrocannabinol (THC)] and a breath alcohol analyzer test. The Medical Ethics Committee approved the study protocol, and written informed consent was obtained from all patients. Procedures were in compliance with the Helsinki Declaration and its latest amendments.

Study design and drug administration

The study was designed as a double-blind, placebo-controlled two-way crossover randomized study. After a training session, the two treatments were administered in 15-day series, separated by washout periods of 6 days (see Fig. 1). Treatment series were randomly assigned to the patients. Daily doses consisted of nocturnally administered 25 mg amitriptyline and a matching placebo, identical in appearance to allow double-blind administration. The dosages of 25 mg were initially prescribed by the physicians of the pain clinics. Subjects ingested the capsules at fixed times each evening. The first dose was administered the night before the first test day. Patients were asked to continue any additional allowed concomitant analgesic drugs at constant dose during the study period. Tasks were performed both after acute (day 1) and subchronic administration (day 15) for both placebo and amitriptyline approximately 16 h after drug administration. It may be noted that mean half-life of amitriptyline and its active metabolite nortriptyline is approximately 36 h, with large interindividual variations.

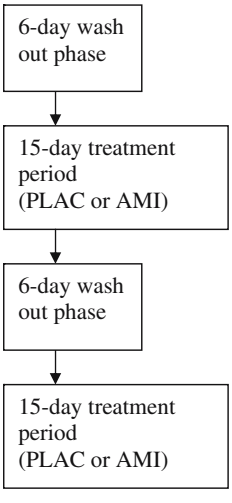

Fig. 1 Design of the study. *PLAC* indicates placebo; *AMI*, amitriptyline

Tasks

In the probe task, difficulty of the primary task was manipulated, while probes were presented. The primary task consisted of an easy and a hard task condition, based on those used in the study of Jonkman et al. (2000). The order of task presentation was counterbalanced across subjects. Each task condition lasted about 10 min and consisted of two blocks. In each block, 90 task and 90 probe stimuli were presented. Each task stimulus was followed by a probe. The task stimuli consisted of four different stimuli, which were purple, red, green, and blue rectangles subtending a height of 5.3° of arc and a width of 4.5° of arc (adapted form Jonkman et al. 2000). All task stimuli were relevant, since a button press was required after each task stimulus presentation. Stimuli were displayed on a monitor positioned approximately 1 m from the subject's eyes. In the easy task, the subject was instructed to press the right-hand button when a blue rectangle appeared and to press the left-hand button when a rectangle of another color was presented. In each block of the easy condition, 45 blue rectangles and 45 nonblue stimuli (15 red, 15 purple, and 15 green) were presented to ensure equal numbers of left- and right-hand presses. In the hard task, the subject had to compare each rectangle with the preceding one. When both stimuli were identical, the right-hand button had to be pressed. When the stimulus was different from the preceding one, the left-hand button had to be pressed. In each block, there were about an equal number of stimuli of each color (22 or 23), and these were randomized such that equal (50%) numbers of right- and left-hand button presses were ensured. The hard task could only be correctly executed if the subject kept a running memory of stimuli.

The probes consisted of 90 stimuli per block. The probes were chosen according to Verbaten et al. (1997) and included three stimulus types: standards, deviants, and novels. Novels were especially included since these were presumed to elicit the most pronounced P3 ERP component. Two types of gratings with different spatial frequency and orientation were used, and these were randomly assigned across subjects as standards (80%) or deviants (10%). Gratings were square-wave, black-on-white, horizontal, high [4.8 cycles per degree (c/d)], or vertical, low (0.6 c/d) spatial frequency stimuli. Standards and deviants subtended a height of 5.7° of arc and a width of 11° of arc. In line with Hoeksma et al. (2004), novels (10%) were unique abstract colored patterns occurring only once during the study. Novels subtended a height of 10.5° of arc and a

width of 11.75° of arc. Stimulus duration was 100 ms for the task stimuli and 924 ms for the probe stimuli. Interstimulus interval (ISI) stimuli were randomized between 1.7 and 2.3 s. The subjects were told that in between task stimuli, other pictures would appear that required attention but no response.

Electrophysiological recordings

An electroencephalogram (EEG) was recorded from tin electrodes by means of an Electrocap. Activity was recorded from the midline electrodes Fz, Cz, Pz, and Oz, which were arranged according to the International 10/20 system. An electrode attached to the left mastoid was used as reference. Horizontal and vertical electrooculograms (EOG) were measured from tin electrodes attached to the outer canthus of each eye and from infraorbital and supraorbital electrodes placed in line with the pupil of the left eye. A ground electrode was placed at the middle of the forehead. All electrodes were filled with electrode paste. Electrode impedances were kept below 5 kΩ. Data acquisition was continuous, with a sampling rate of 250 Hz and a gain of 1,000. Signals were amplified online with a high-pass frequency filter of 0.05 Hz and a low-pass filter of 100 Hz. Offline, data were filtered with a 30-Hz 24 dB/octave low-pass filter and epoched, starting 100 ms before stimulus onset and lasting for 800 ms after stimulus onset.

Subjective assessment

Subjective measures were assessed on each test day. The following scales were administered to assess depression and anxiety: Center for Epidemiologic Studies Depression Scale (CES-D; Beekman et al. 1997), Spielberger State–Trait Anxiety scales (STAI; Spielberger 1983), and five subscales (Depression, Anger, Tension, Vigor and Fatigue) of the shortened version of the Profile of Mood State (POMS; McNair et al. 1971). Pain intensity was assessed using the Visual Analog Scale (VAS) from the McGill Pain Questionnaire (MPQ; Melzack 1975). The left end of the 100-mm scale was labeled "no pain," and the right end was labeled "unbearable pain." To monitor possible side effects, adverse-symptom checklists were administered each test day. This checklist included symptoms of drowsiness, concentration problems, headache, dizziness, feeling irritable, feeling dazed, gastrointestinal disturbances, and dry mouth.

Procedure

A training session was held to familiarize the subjects with the procedure, and subjects were screened for their ability to perform the hard task (80% correct criterion). During this session, no EEG was recorded, and no novel stimuli were shown. After this training session, the experiments took place on four different days. Patients were asked to abstain from smoking for at least 3 h prior to the experiment. They did not use caffeinated drinks or alcohol on the day of the experiment. Upon arrival at the laboratory, inclusion and exclusion criteria were verified. After attachment of the electrode cap and EOG electrodes, subjects were seated in a dentist's chair in an acoustically shielded and dimly lighted room. The chair was adjusted so that the subject's head was positioned parallel to the monitor. Instructions for tasks were presented on the monitor. After the instruction, subjects had to perform a short practice session of 20 stimuli. Next, the task was started. Subjects were instructed to move as little as possible during the task and to keep their eyes fixed on the fixation dot on the center of the screen. After each block, the experimenter entered the room and gave instructions for the next block.

Data analysis

Reaction times were calculated for correct button presses occurring between 150 and 1,700 ms after stimulus onset. Faster or slower responses were discarded. Error rates were computed as total errors divided by the sum of errors and correct responses, and omission rates were computed as total omissions divided by the sum of errors, omissions, and correct responses, excluding RTs lower than 150 ms and higher than 1,700 ms.

Electroencephalogram and EOG data were analyzed offline using Analyzer software (Brain Products GmbH). All signals were baseline-corrected on the basis of the 100-ms prestimulus interval. EEG epochs with amplifier blocking, artifacts, or flat lines were detected and omitted from further analysis. Ocular artifacts were estimated and subtracted by time domain regression analysis (Gratton et al. 1983). Average waveforms were computed separately for each experimental drug condition (amitriptyline and placebo), administration phase (acute and subchronic), stimulus type (task stimuli, standards, deviants, and novels), and the four midline electrodes (Fz, Cz, Pz, and Oz). Task ERPs were computed by averaging trials with a correct response. Probe ERPs were computed by averaging only trials in which, in agreement with instructions, no response was given (and the preceding task stimulus was correctly responded to) to assure attentional investment in the task procedure. The number of trials included in average ERPs was at least 128 for the task stimuli, 13 for the novels, 12 for the deviants, and 115 for the standards.

Mean area P3 activity was computed in three 100-ms segments in the 300–600 window. These segments were chosen after visual inspection of the grand average waveforms. Area measures were chosen since the P3 is a very broad wave often composed of multiple peaks that are not covered by single-peak scoring.

Statistical analysis

Repeated-measures univariate analyses of variance (ANOVAs) were performed for all data. Because of the small sample size, a planned comparison procedure was chosen.

The acute effect of amitriptyline was tested against acute placebo administration, and subchronic amitriptyline was compared to subchronic placebo administration.

Within-subject factors for the performance data were drug (two levels, amitriptyline and placebo) and task (two levels, easy and hard). Further, all statistical analyses initially included the between-subject factor order of drug administration (two levels, first amitriptyline or first placebo). This between-subjects factor was included in the analyses to investigate the possibility of increased variance of within-subject effects due to the difference in order of drug administration. If order of drug administration had no effect, it was removed from the model. Statistical analysis of data that were not normally distributed was performed using the Wilcoxon nonparametric test for two related samples.

Statistical analyses on ERP data were performed separately on mean amplitudes for the P3 component for three 100-ms windows: 300–400, 400–500, and 500–600 ms. The analysis of ERP data included the within-subject factors drug (two levels, amitriptyline and placebo), task (two levels, easy and hard), and lead (four levels, Fz, Cz, Pz, and Oz). In addition, for the pooled analysis of probe stimuli, the within-subjects factor stimulus type (three levels, novels, deviants, and standards) was included. Subsequently, the aim of the conducted post hoc tests was to test differences at each probe type and lead separately. As visual inspection of the ERP data suggested some additional drug effects on components preceding the P3 in time, these were explored. For all tests, a critical α-level of .05 was used. Statistical analyses were performed with SPSS 11.0.1 for Windows.

Results

The number of patients who took part in this study was low due to difficulties in recruiting patients. Six patients [three men and three women, mean (±SD) age 52 (3.4) years, age range 42–58 years, and mean weight 82 (7.2) kg] completed the study. Demographic variables of patients are depicted in Table 1.

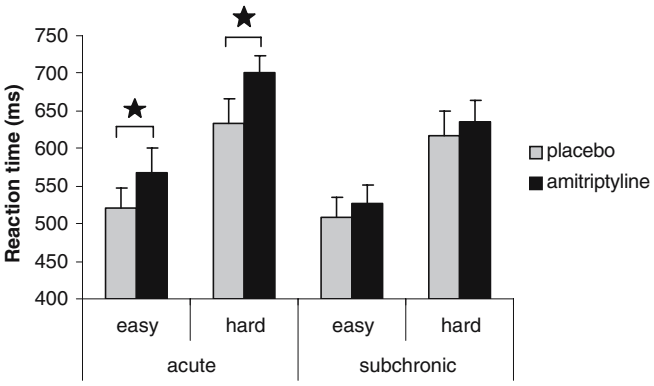

Fig. 2 Mean reaction time as a function of drug and task conditions. Significant difference is indicated by *

Performance

Reaction times

In the acute phase, statistical analysis revealed a significant effect of drug on RTs [$F(1,5)=19.05$, $p<0.007$], indicating that after acute amitriptyline administration, RTs were significantly longer compared to placebo (see Fig. 2). No significant main effect of drug was found in the subchronic phase. As expected, a significant task effect was found in both the acute [$F(1,5)=67.12$, $p<0001$] and the subchronic phase [$F(1,5)=56.73$, $p<0.001$], indicating that in the hard task condition, RTs were significantly longer compared to the easy task condition. These findings confirmed the effectiveness of the task difficulty manipulation. A significant interaction between drug and task was found neither after acute administration nor after subchronic administration.

Errors and misses

No significant effects were found for drug or for an interaction between task and drug on error rates. A significant main effect of task was found for error rates, both after acute and subchronic administration; more errors were made during the hard compared to the easy task [$F(1,5)=37.15$, $p<0.002$ and $F(1,5)=31.62$, $p<0.002$, respectively]. No effects were found for omission rates. Mean and standard

Table 1 Subjects' demographics

Patient number/ sex/age (years)	Diagnosis	Duration of pain complaints (months)	Duration of AMI use (months)	Concomitant analgesic medication
1/M/51	Lumbal radiculopathy	96	6	Ibuprofen
2/F/54	FBSS with sacral radiculopathy	36	18	Rofecoxib, paracetamol, naproxen
3/F/58	FBSS and spinal stenosis	60	12	Rofecoxib, paracetamol
4/M/52	Mixed nociceptive and neuropathic local pain in arm	24	7	Rofecoxib, lidocaine crème
5/F/54	FBSS	72	6	Paracetamol, ibuprofen
6/M/42	Cervicobrachialgia	30	5	Naproxen, acetylsalicylic acid, paracetamol

AMI Amitriptyline, *FBSS* failed back surgery syndrome

Table 2 Mean (SE) reaction time, error rates, and omission rates for the easy and hard tasks in the amitriptyline and placebo conditions after both acute and subchronic administrations

	Placebo		Amitriptyline	
	Acute	Subchronic	Acute	Subchronic
Reaction times (ms)				
Easy	520.5 (26.7)	508.7 (26.5)	567.5 (32.7)	526.6 (24.6)
Hard	634.3 (32.2)	616.1 (33.6)	701.2 (21.2)	635.5 (28.1)
Error rates (%)				
Easy	0.8 (0.3)	0.6 (0.2)	1.1 (0.4)	1.0 (0.2)
Hard	2.6 (0.4)	2.6 (0.5)	3.7 (0.5)	2.8 (0.2)
Omission rates (%)				
Easy	1.1 (0.6)	0.8 (0.5)	3.0 (1.8)	0.6 (0.3)
Hard	0.4 (0.3)	1.0 (0.5)	1.9 (1.1)	0.8 (0.5)

errors for behavioral measures for each drug and task condition and administration phase are presented in Table 2.

ERP P3 analyses

Task stimuli

Figure 3 shows the grand average waveforms for the task stimuli at the Pz lead. No main effects of drug, an interaction between task and drug, or an interaction between drug and order of drug administration were found for both acute and subchronic treatment. Statistical analysis revealed a significant main effect of task for task stimuli in the 400- to 500-ms window after both acute [$F(1,4)=8.14$, $p<0.046$] and subchronic administration [$F(1,5)=7.82$, $p<0.038$]. In the hard task condition, P3 amplitude was significantly reduced compared to the easy task condition. No significant interaction between task and lead was found; however, exploratively, subsequent analyses were performed to examine on which leads this task effect was most prominent. These analyses showed that after acute ad-

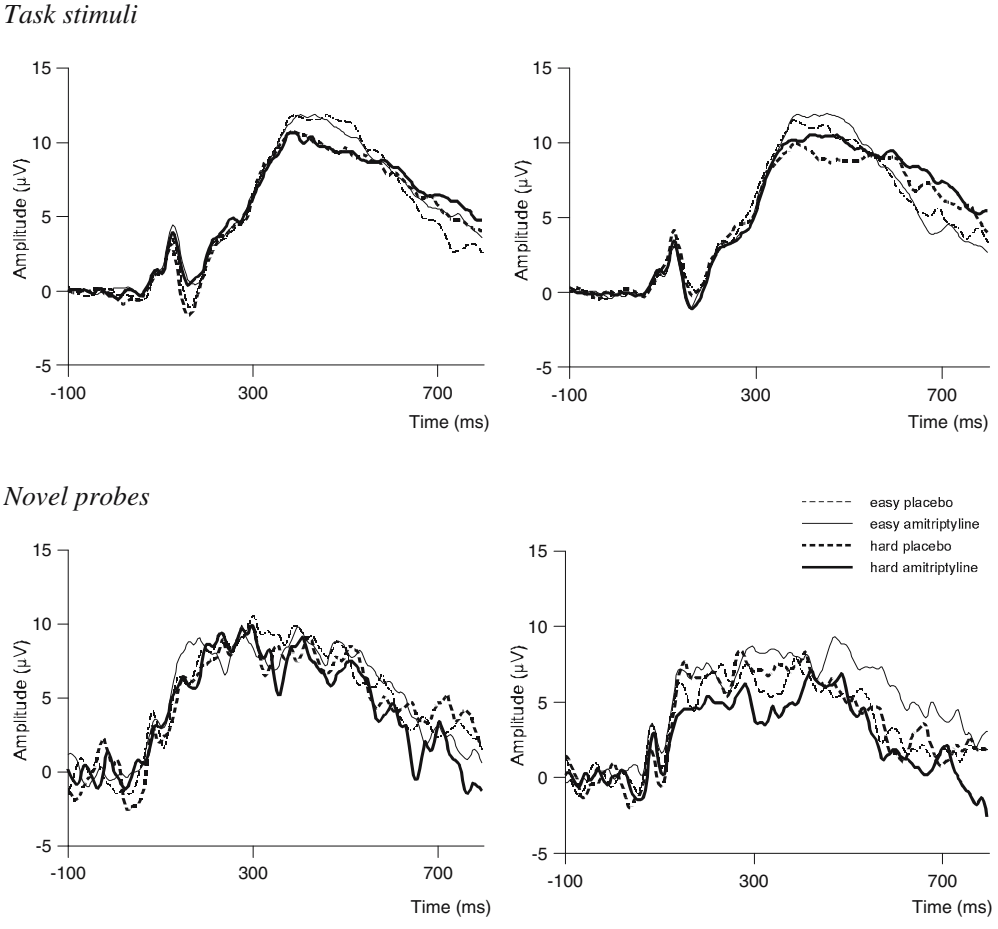

Fig. 3 Grand average waveforms at the Pz electrode in the easy and hard conditions. *Upper panel*, task stimuli; *lower panel*, novel probes; *left panel*, acute treatment; *right panel*, subchronic treatment

ministration, significant effects were found at Pz [$F(1,5)$= 8.94, p<0.030] and after subchronic administration at Cz [F (1,5)=8.92, p<0.031) and Pz [$F(1,5)$=9.20, p<0.029]. No significant effects were found on other leads.

After visual inspection of the grand average waveforms of the task stimuli (shown in Fig. 3), the visual N1 component was analyzed at Pz (140–200 ms) and Oz (130–180 ms) to examine if this component was significantly different under amitriptyline. Statistical analysis yielded a trend toward significance for the drug effect after acute administration for the N1 component at Pz [$F(1,4)$=7.42, p<0.053], but not for Oz. At Pz, N1 amplitude was more negative in the placebo than in the amitriptyline condition. No significant effects for the N1 amplitude were found after subchronic administration.

Probe stimuli

No main effects of drug or task were found for pooled probes, both after acute and subchronic treatment. Significant interactions between drug and order of drug administration were found for the acute administration phase in all three windows (p<0.035), but not for the subchronic administration phase. No interaction between drug and task was found after acute administration. However, after subchronic treatment, a significant Drug × Task interaction was found, both in the 300- to 400-ms [$F(1,5)$= 10.30, p<0.024] and 500- to 600-ms [$F(1,5)$=8.30, p<0.035] windows. After subchronic amitriptyline treatment, P3 amplitude was larger in the easy compared to the hard task condition, which was significant in the 500–600 window [$F(1,5)$=7.50, p<0.041]. This was not found after placebo treatment. This effect implies that the difference between task conditions was increased under amitriptyline on day 15. No significant interaction between drug, task, and stimulus type was found; however, exploratively, subsequent analyses were performed to elucidate the most prominent probe and the most prominent lead. When analyzing each probe type separately, these Drug × Task effects appeared prominent for the novel probes but not for the standards and deviants. After subchronic treatment, a trend toward significance was found for the novels for the interaction of Drug × Task in the 500- to 600-ms window [$F(1,5)$=5.47, p<0.066]. Moreover, at Pz, where the largest effects were expected, this interaction was significant [$F(1,5)$= 7.35, p<0.042). Further analysis showed that amitriptyline increased P3 amplitude in the easy condition [$F(1,5)$=7.50, p<0.041] but not in the hard task condition. No significant Drug × Task interactions were found for the other leads. Grand average waveforms for the novel stimuli at the Pz electrode are displayed in Fig. 3.

Subjective assessments

Overall, participants scored within the normal range on assessments of depression and anxiety (CES-D, STAI, and POMS). No significant differences were found between treatments in the acute or subchronic phase on these measures. Pain intensity scores did not differ between treatment conditions, neither in the acute nor in the subchronic phase (Fig. 4). Reported adverse events were mild and did not differ in incidence and intensity between treatments.

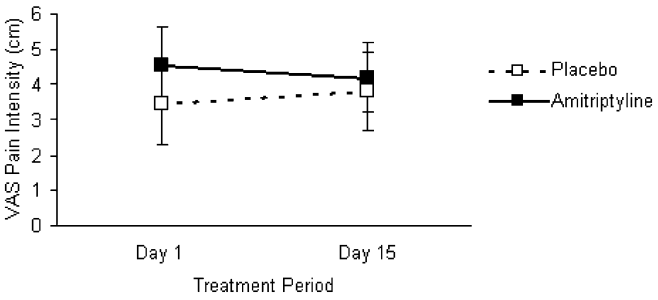

Fig. 4 Mean (±SE) VAS pain intensity scores in centimeters after acute (day 1) and subchronic (day 15) treatment in the amitriptyline and placebo conditions

Discussion

The aim of this study was to investigate the effect of low-dose, 25 mg amitriptyline administered nocturnally on attentional processing capacity in neuropathic pain patients. To this end, a probe task was used in which task-irrelevant probe stimuli were presented against a background of an easy and hard task, varying in their demand on capacity resources. The increasing demands for processing capacity should be reflected in behavioral task performance. Indeed, in the hard task condition, error rates were significantly higher, and RTs were significantly longer, both after acute and subchronic treatment. Hence, task difficulty was successfully manipulated. With regard to the effects of acute administration of amitriptyline, the results showed that even after a low nocturnally administered 25-mg dose, performance at the behavioral level was impaired. Acute amitriptyline significantly increased RTs for both the easy and hard tasks. In line with previous studies (e.g., Robbe and O'Hanlon 1995; van Laar et al. 2002), it appeared that tolerance developed to these sedative effects. No impairments were found after 2 weeks of amitriptyline treatment for RTs, error rates, or omission rates. Overall, relatively few adverse events were reported in the amitriptyline treatment condition, both after acute and subchronic treatment, and no differences with placebo were found.

Task effects were also present in the ERP data of task stimuli. In the 400- to 500-ms latency window, P3 amplitude to task stimuli were significantly reduced in the hard compared to the easy task condition (after both acute and subchronic administration) independent of drug administration, and as expected, mainly at the Pz electrode. Previous studies that applied the probe task have also found the most prominent effects of the primary task at the Pz electrode. However, in contrast to the results of the present study, frequently, an increase in P3 amplitude is found when the difficulty level of the primary task increases, reflecting that more attentional resources are invested in

the harder task (Wickens et al. 1983; Jonkman et al. 2000; Hoeksma et al. 2004). Nevertheless, it has been previously reported that P3 may also decrease with increasing task demand. This is most commonly found in studies utilizing visual search tasks (Kok 2001). In these tasks, the decrease in P3 amplitude is thought to reflect a negative memory-related search wave overlapping the P3 amplitude (Jonkman et al. 2000). Although the task effects to the task-relevant stimuli are difficult to interpret and anything but straightforward, it was found that amitriptyline did not interact with task performance for these task-relevant stimuli. This is consistent with the results of the behavioral data.

Event-related potentials to the task-irrelevant probes were used to assess the resource demands imposed by the primary task and the influence of amitriptyline on this process more purely, since they are relatively free from target-related processes (Kramer et al. 1995). P3 amplitudes elicited by task-irrelevant probes are thought to reflect a trade off in processing demands. When demands of the primary task increases, the P3 amplitude to the probes generally decreases, especially for the rare novel probes, which is thought to reflect that there is less spare resources to invest in the secondary task (Wickens et al. 1983). As noted before, it was hypothesized that if amitriptyline would affect attentional capacity, P3 amplitude would decrease in the hard relative to the easy task condition, and P3 would decrease more in the amitriptyline compared to the placebo condition. However, in contrast to expectations, in the present study, no effects were found on P3 for the task-irrelevant probe stimuli after acute amitriptyline administration. Moreover, it was found that after subchronic amitriptyline treatment, the Pz P3 amplitude was increased in the easy task compared to the hard task condition, indicating that the effect of task load to novel probes was increased under amitriptyline on day 15. Apparently, after subchronic treatment of amitriptyline, patients under amitriptyline had more resources available to process the novel probe compared to placebo, especially when the task at hand was easy. Thus, the expected decrease in P3 amplitude to probe stimuli with increasing task load under amitriptyline, reflecting a depletion of resources, was not found. In contrast, in particular for the most prominent probe, i.e., the novel probe, it was found that P3 amplitude was higher in the easy compared to the hard task condition under amitriptyline compared to placebo. These results suggest that patients may actually benefit from repeated amitriptyline treatment since the increased amplitude found after amitriptyline treatment was not observed in the placebo condition. Under subchronic amitriptyline treatment, patients show the "normal" pattern of a larger investment of processing capacity in task-irrelevant probe stimuli with lower demands of the primary task (Wickens et al. 1983). Without amitriptyline treatment, patients exhibit a different allocation strategy, resulting in an absence of additional probe processing during the easy task condition. A possible explanation of this perceived difference between amitriptyline and placebo treatment may be that patients are likely to have increased pain during placebo treatment, which might have influenced allocation of resources. This explanation is, however, explorative since no significant differences on the pain intensity scales were found between treatments. Future research should address this differentiation between effects of pain and those of amitriptyline with larger samples. Overall, the results suggest that amitriptyline does not negatively affect attentional processing capacity in patients with chronic pain.

More exploratively, effects on ERP components preceding the P3 were examined for appearance of drug effects. For the task stimuli, independent of the difficulty of the task, the N1 amplitude was smaller at Pz after acute administration of amitriptyline relative to placebo. This early visual effect was not observed after subchronic amitriptyline administration. The decreased N1 amplitude for primary task stimuli may reflect that these stimuli were processed to a lesser extent under acute administration of amitriptyline, which might explain why acute amitriptyline did affect behavioral measures. However, possible induced deficits in early visual processing of stimuli need to be addressed in future studies.

A limitation of our study is the small sample size. The low amount of subjects might have led to low power for finding statistically significant results. It appeared very difficult to find patients using amitriptyline as psychoactive monotherapy. Most patients in clinical practice are treated with multiple psychoactive drugs simultaneously. In this context, it is important to note that there may have been a selection bias with respect to participating patients. Patients who took part in the study may have had less severe pain than the majority of patients who use amitriptyline since they were effectively treated with only one psychoactive drug. Indeed, pain intensity ratings were unexpectedly low and, moreover, not reduced under amitriptyline treatment compared to placebo. This latter finding is even more remarkable since the participating patients were adequately treated with amitriptyline for 5 months or more prior to study participation. We do not have a clear explanation for this observation, but it cannot be ruled out that patients selectively participated to find out if they could do without their medication. Another (speculative) possibility is that no difference in pain relief was found due to carryover effects of amitriptyline that relieve pain for an extended period of time, at least beyond the 6-day washout phase. Moreover, as mentioned before, the small sample size might have resulted in low power for finding statistically significant results.

The fact that there was no task effect on the probe ERPs in the placebo conditions leaves the possibility that no capacity trade off might have occurred, and this might have been due to the fact that the task was not challenging enough to deplete resources in the hard task. Future studies applying more difficult task conditions are necessary to address this problem. Further, it should be noted that our findings are generalizable to the pain patient population only.

The use of paracetamol and/or NSAIDs was not prohibited in this study to allow escape medication when needed and to avoid drop outs because of severe pain. It is well known that NSAIDs and/or paracetamol have poor analgesic efficacy in the treatment of neuropathic pain (e.g., McCleane 2003); therefore, this cannot explain the low pain intensity scores found in this study. Moreover, the use of

NSAIDs and/or paracetamol was consistently used at constant dose throughout the study period and can therefore not account for performance effects.

This study confirms earlier findings that acute administration of 25 mg amitriptyline affected RT performance. No such effect was observed after subchronic treatment. ERP results suggested that acute amitriptyline did not affect processing capacity negatively, and that patients might actually benefit from amitriptyline after repeated administration. Behavioral impairment found after acute amitriptyline administration could therefore not be related to an impairment in attentional capacity.

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