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Clonidine effects on pain evoked SII activity in humans

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Abstract

We investigated pain evoked activity in the human secondary sensory cortex (SII) following clonidine administration in six healthy volunteers using multi-channel magnetoencephalography (MEG). Pain was elicited by electrical shocks applied intracutaneously to the fingertip. Subjects rated pain intensity and perceptions of tiredness and passiveness by numerical ranking scales. Each subject underwent two investigations, one week apart from each other, with clonidine doses of 1.5 or 3.0 µg/kg, administered intravenously in a random order and double-blinded. We applied a total number of seven blocks, each consisting of 60 painful stimuli, with one adaptation block, one pre-medication block, four post-medication blocks and one recovery block at the end of the session. MEG data were analysed by dipole reconstruction using CURRY^R (Neuroscan, Hamburg) software package. Cortical activity in the contralateral SII cortex appeared with peak latencies of 118.5 ± 10 ms. This activity was significantly reduced by clonidine, in parallel with a reduction of pain intensity and enhancement of subjective tiredness and passiveness. There was, however, no significant correlation between MEG and subjective effects. Although both clonidine doses had similar effects, the higher dose induced longer changes. Results indicate that intravenous clonidine is able to relieve pain, but the exact mechanism of clonidine at the level of the SII cortex remains unclear. It is possible that clonidine interacts with the brainstem ascending system regulating vigilance and arousal which would explain the observed decrement of pain induced activity in SII. An additional more specific analgesic action at spinal level cannot be excluded.

Keywords: Pain; SII cortex; Clonidine; Vigilance; Analgesia; Dipole reconstruction; MEG

1. Introduction

The perception of pain contains sensory, cognitive and affective components (Melzack and Casey, 1967). It is possible to assign some of these components to circumscript activities in different brain regions (Talbot et al., 1991; Casey et al., 1996; Bromm et al., 2000).

According to their main neuronal input from lateral thalamic nuclei, the primary (SI) and secondary somatosensory cortices (SII) are parts of the lateral pain system (Treede et al., 2000) which governs mainly sensory-discriminative functions, i.e., the processing of information about duration, strength and location of pain. In contrast, the cingulate gyrus is part of the medial pain system and plays an important role in the cognitive and affective aspects of pain perception (Bush et al., 2000). Most knowledge about SII comes from invasive animal studies focussing on tactile functions (for review see

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Burton et al., 1982). With the introduction of biomagnetometry, the human SII cortex can be investigated noninvasively for the first time, especially in the context of pain (Hari et al., 1983a,b; Laudahn et al., 1995; Kakigi et al., 2000). Pain relevant SII areas are located superficially in the cortex, and the respective columns show a tangential direction to the head surface, allowing the detection of relatively large magnetic fields during neuronal activity (see, for example, Hillebrand and Barnes, 2002). Pain related SII activity has meanwhile been described by many authors using functional brain imaging methods, in particular multi channel MEG recordings. The activity starts between 90 and 150 ms after the pain stimulus, depending on the body site and activated nerve fibre spectrum (Howland et al., 1995; Bromm et al., 1996; Kakigi et al., 1996; Lenz et al., 1998; Frot et al., 1999; for review see Bromm and Lorenz, 1998). Also, it is well known that pain-induced SII activity depends strongly on the vigilance level and the attentional state of the brain (Bromm et al., 2000; Hämäläinen et al., 2000; Nakamura et al., 2002).

The following study addresses the question whether pain evoked SII activity is altered by clonidine, an α2-agonist with both antinociceptive and sedative properties. Clonidine is typically used as co-analgesic in post-operative pain management (see, e.g., Bischoff and Kochs, 1993; Kanui et al., 1993; Eisenach et al., 2000). Using dipole reconstruction analysis of magnetic brain maps gathered from multichannel MEG, we investigated the effects of two different doses of intravenously administered clonidine on the SII-Cortex.

2. Methods

2.1. Subjects and test procedure

The study was performed on seven healthy male students (six right handed, one left handed) with written informed consent (age 26 ± 3 years, height 183 ± 7 cm, weight 76 ± 5 kg) after being approved by the Institutional Ethics Committee. Control of standard clinical and neurological status, serum chemistry, and MRI scan of the brain yielded normal findings and there was no history of neurologic or psychiatric abnormalities. The MRI scan was additionally used to calculate the dipoles in the individual anatomy. One subject was discarded, because of strong artefacts during MEG recordings. We tested subjects in two separate sessions, one week apart from each other, with two doses of clonidine (1.5 and 3.0 μg/kg), administered intravenously. The order of doses was randomized and double-blinded. Subjects underwent a clinical examination before and 3 h after medication in which blood pressure, blood oxygenation and heart rate was monitored (Jenacor, Jena, Germany). Pain was induced according to the intracuta-

neous pain model (Bromm and Meier, 1986; Scharein and Bromm, 1998). Briefly, a thin needle electrode was fed through a hole punched into the horny skin of the tip of the middle finger of the non-dominant hand and an electrical pulse (5 ms duration) delivered to the nearest neighbourhood of nociceptors. We applied two different stimulus intensities according to 2 (I_1) and 3 (I_2) times individual pain threshold (I_p) the latter being determined by a series of increasing stimulus intensities and decreasing stimulus intensities at the beginning of each session. The subjects had to rate the stimulus intensity according to a numerical ranking scale (NRS) with values from 0 to 10. Values of more than three described a painful sensation and determined the pain threshold I_p. The average pain threshold intensity was 0.2 mA (± 0.07 mA standard deviation).

During the experiments subjects lay in a noise-reduced, electrically and magnetically shielded chamber containing the cryostat supplied with 31 gradiometers. The stimuli were given in blocks of 60 with the two intensities I_1 and I_2 in a quasi random sequence; the inter-stimulus interval varied between 6 and 10 s. Thus each block lasted approximately 12 min. Recordings of the single trials were averaged within each block as average block data to reduce the signal to noise ratio. On each investigation day, seven blocks of stimuli were applied with intervals of 3–5 min between the first six blocks. The first one (block 0) was done for adaptation only and excluded from further evaluation, to minimize the largest source of variability due to habituation (Bromm and Lorenz, 1998). The next block served to achieve pre-medication values (block PRE). Immediately after administration of clonidine, six consecutive blocks explored the effects over a post-medication time period lasting from 0 min (POST1) to 55 min (POST4) after medication. At the end of the session (90 min after medication) the last stimulus block was performed (RECOVERY). Three seconds after each pain stimulus, a tone prompted the subjects to rate their sensation using the NRS. Moreover, subjective tiredness and passiveness was measured by visual analog scales (0–100). Higher values describe a greater extent of tiredness and passiveness, whereas values around 0 describe no tiredness and passiveness at all. The subjects were asked to describe their perceptions before the first block as well as 60 and 120 min after clonidine injection.

2.2. Data recording and evaluation

MEG data were measured with a 31-channel biomagnetometer (Philips, Hamburg); the gradiometers were centred over the hemisphere contralateral to the stimulated side (C3, C4). A 32 channel EEG was also recorded to control for changes in vigilance. Responses were restricted to a frequency band between 0.3 and 100 Hz and digitized at a sampling rate of 200 Hz. A

spherical model obtained from the individual MRI scans was fitted to the head shape of each subject. Further dipole reconstructions were calculated with the CUR-RY[R] software package (Neuroscan, Hamburg). After visual artifact control (on the average less than 10% of all recordings were discarded), 70 Hz low pass filtering and common mode rejection, data of the pre-medication blocks were subjected to the one moving dipole approximation, which is sufficient for SII evaluations as determined by earlier studies (Bromm and Lorenz, 1998). With a relative maximum of the mean global field power (GFP) between 80 and 160 ms, the best fitting dipole had to fulfil the following attributes: a goodness of fit (GOF) better than 90%, a spatial stability (D) lower then 10 mm, and a lifetime of at least 15 ms. Spatial stability (D) describes the euclidean distance of the dipole coordinates between adjacent sample points. Life-time means that these parameters have to occur for at least 15 ms. If these attributes were fulfilled, the dipole could be regarded as stable over time. As a last step, all dipole coordinates were transformed into the Talairach coordinate system (Talairach and Tournoux, 1988), using the individual head morphology.

The dipole found in the MEG data block PRE was then fixed for analysis of the cortical activity after clonidine administration. This had to be done, since the evoked fields were drastically reduced under clonidine with a low signal to noise ratio. Moreover, we did not assume that clonidine shifts the location of pain-induced SII activity. For further statistical analysis SPSS 10.0 was used (SPSS, Chicago, IL). After first testing all data for normal distribution using a Kolmogorov–Smirnov test, the global data set was subjected to a two factorial analysis of variance (ANOVA). Significant results were further analyzed with paired student t-tests for dependent samples. Correlations between SII dipole strength and pain perception were calculated as well.

3. Results

Results of a single subject (HE) with the original recorded data of the pre-medication block are shown as butterfly plot in Fig. 1A. It illustrates a maximum of evoked magnetic activity at approximately one hundred ms after stimulus onset. Fig. 1B displays the isocontour map of this field at peak maximum of 105 ms projected on the individual's head (obtained from the MRI scans). It indicates a distinct inversion in polarity (continuous lines indicate outward fields, dashed lines field entrances) that is characteristic for a dipolar field. Source reconstruction of this evoked field revealed a dipole, the location of which is shown in Fig. 1C. This dipole had a maximal dipole strength ($Q = 29.1$ μA mm) at 105 ms and a goodness of fit (GOF) of 98.3% between measured and calculated fields around peak latency
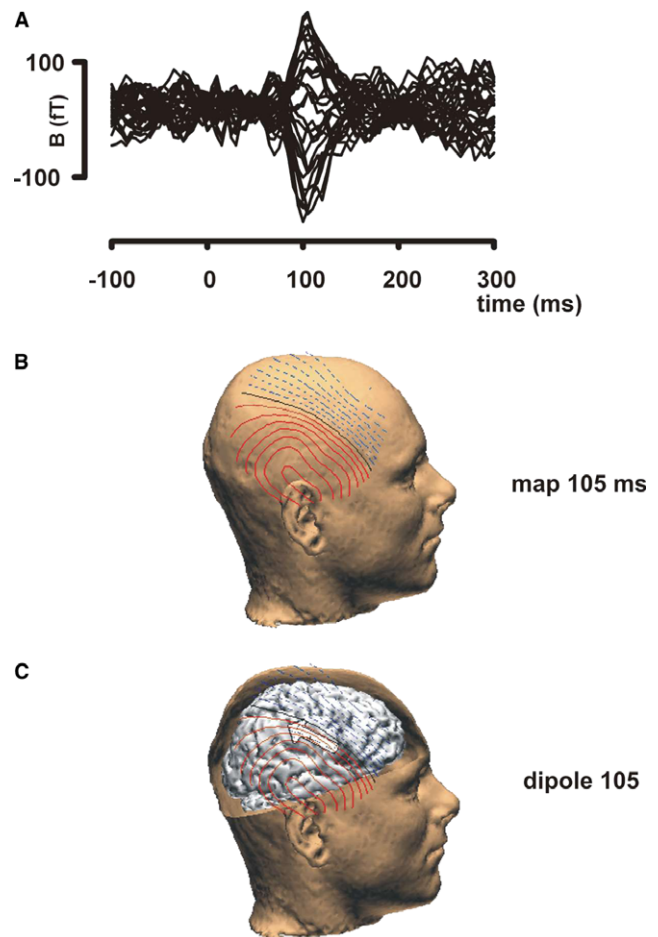

Fig. 1. Data of the premedication block, single subject HE. Above (A) is shown the butterflyplot of all 31 MEG channels with two field maxima. The isocontour map of the second maxima after 105 ms is shown in the middle (B) and projected on the subjects head. Dipole reconstruction of this field with interindividual anatomy parameters found a dipole in SII (C).

time. The coordinates of the identified dipole in the Talairach system were: $X = 54.1$; $Y = -9.0$; $Z = 22.6$, which is clearly in the SII area of the dominant hemisphere (Table 1) The dipole direction was parallel to the cortex surface and oriented from superior to ventral. It should be noted that a similar dipole appears in the ipsilateral hemisphere (bilateral SII co-activation; Kakigi et al., 1995; Bromm et al., 2000) but cannot be identified with only one cryostat positioned over the C3 location of the 10–20 system, as used in this study.

Similar findings were made in all subjects regarding the pre-medication blocks of the study. The peak maxima in mean global fields varied from subject to subject in a range between 90 and 130 ms. Results are given in Fig. 2, illustrating the high re-detection accuracy of measurements. In principle, all dipoles were found in SII; only one of the 14 pre-medication blocks (subject PR, day 2) failed to be localized within SII. The dipole coordinates and additional parameters are summarised

Table 1
Dipole coordinates in the Talairach-system (x, y, z); dipole strength (Q); mean global field maxima (MGF); goodness of fit (GOF) and the latency time (time) are shown for both medication conditions (µg/kg) for each subject at the premedication block

Subject	(µg/kg)	x (mm)	y (mm)	z (mm)	Q (µA mm)	GOF (%)	MGF (fT)	Time (ms)
HE	3	54.1	−9	22.6	29.1	98.3	134	100
HE	1.5	41.7	−16.3	27.7	21.8	98.7	92.5	105
ME	3	61.9	−16.6	9.1	11.8	96.1	61	120
ME	1.5	55.5	−11.6	5.2	27.3	97.3	106	120
PR	3	55.3	10.8	32.5	8.84	93.8	64.4	130
PR	1.5							
SA	3	35.5	−5.6	16.3	44.4	98.7	118	105
SA	1.5	37.4	−4.8	21.2	29.1	98.6	84	115
WA	3	58.8	−5.1	38.3	8.05	86.9	46.1	125
WA	1.5	56	−1.5	26.8	6.2	83.1	31.8	125
KU	3	(−)60.1	−3.9	17.3	35.2	97.6	139	125
KU	1.5	(−)54.4	−10.4	13.1	33.2	98.8	128	125
Mean		52.2	−5.3	21.9	22.57	91.75	84.61	118.75
SD		8.8	8.9	10.1	12.38	13.17	42.26	10.25

Values are the mean value with standard deviation.

in Table 1. In general, the intra-individual dipole site variations were within the spatial resolution of our techniques (<6 mm, for further details see Fuchs et al., 1998).

The effects of clonidine are shown in Fig. 3 for subject HE. Already 20 min after medication, within stimulus block POST2, pain induced SII activity disappeared completely. As a consequence the signal to noise ratio was very low after clonidine application in all subjects. In order to calculate a reasonable dipole model, we had to apply the fixed dipole approximation (see methods) with the individual coordinates given in Table 1;

in case of PR, day 2, we used those coordinates found in day 1. In this way the clonidine induced reduction in SII dipole-strength was quantified. The effects of the two clonidine doses upon the SII dipole strengths are shown as a function of medication time in Fig. 4A. At the higher dose of clonidine. the dipole strength decreased from 22.9 ± 15.4 µA mm in the PRE block to 19.2 ± 14.5 µA mm in POST block1 and 5.5 ± 14.5 µA mm in POST block2, which was 22% of the PRE value. Post Block 3 and 4 and the REC Block yielded a gradual recovery of the dipole strength to mean values of 7.9 ± 4.3, 13.1 ± 11.4 and 11.4 ± 9.0 µA mm, respectively. A
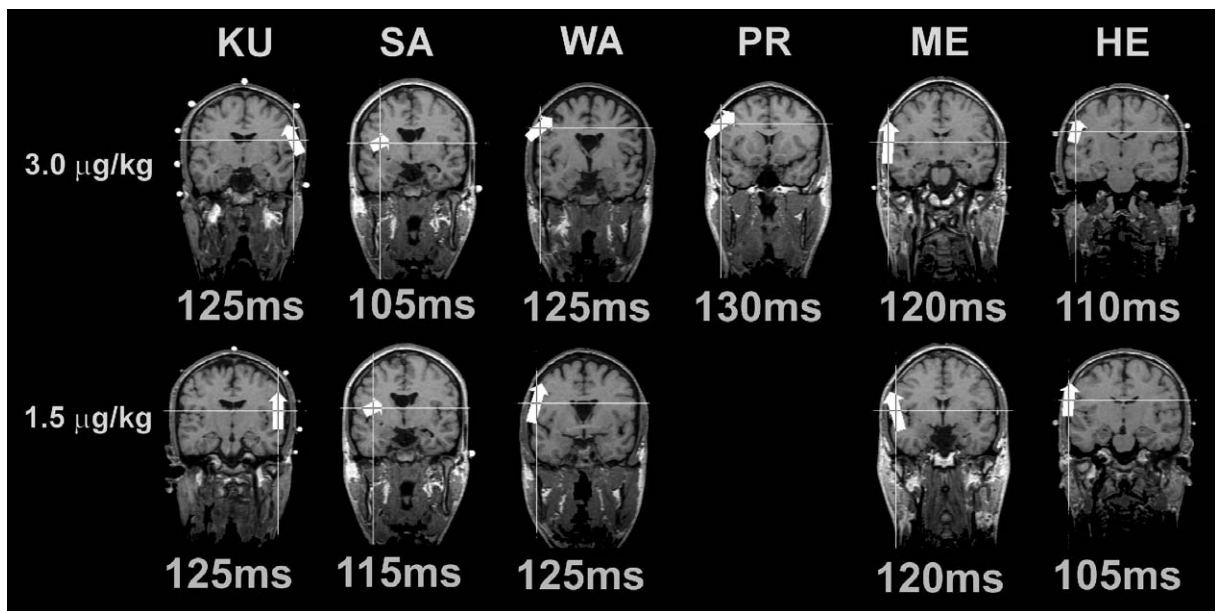

Fig. 2. Dipole localisations of all subjects were found in SII. It is only shown the premedication block of the experiment conditions with higher (3.0 µg/kg) and lower (1.5 µg/kg) clonidine dose, which was applicated after this block. These interindividual dipole localisations were fixed for further source analysis to investigate the effect of clonidine. Subject KU was left handed, so the dipole was found in the contralateral side.
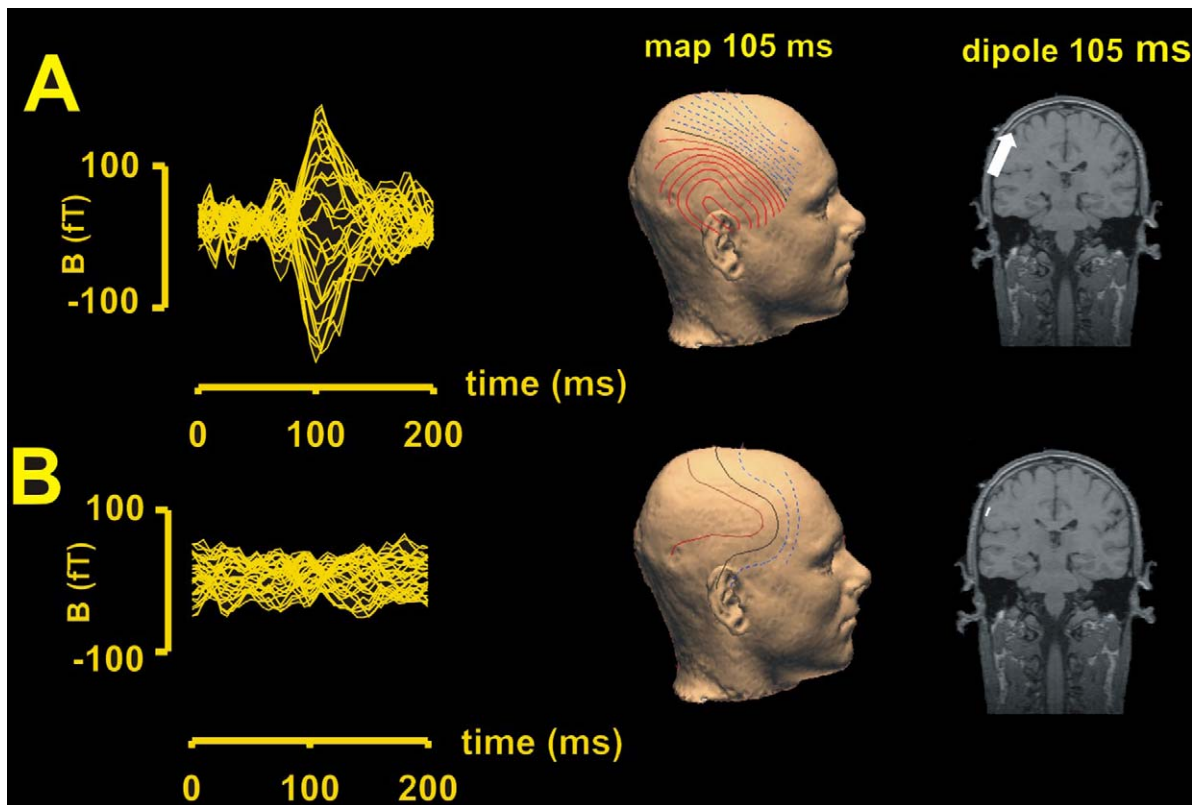
Fig. 3. Butterfly plots with corresponding iso contourmaps and dipole localisations are shown for the premedication block (A) and 20 min after clonidine application (B). The SII-activity is reduced after clonidine application. Shown is subject HE.

similar time course of change occurred for the lower dose. The dipole strength decreased from 22.2 ± 9.9 µA mm in the PRE block to 13.6 ± 10.0 µA mm in POST block1, to 6.8 ± 5.1 µA mm in POST block2 and to 6.4 ± 2.9 µA mm in POST block3, the latter being 28% of the PRE value. Again, there was a recovery of the dipole strength to 7.7 ± 5.6 µA mm in POST block4 and 16.9 ± 14.6 µA mm in the REC block. Thus, clonidine dose had no effect on the reduction of the SII dipole strength, but appeared to extend its duration.

Fig. 4B shows the pain ratings for all subjects, which were measured during the treatments in each individual, as described above. At the higher dose of clonidine, pain ratings decreased from 4.7 ± 0.7 in the PRE block to 3.6 ± 0.4 in POST block1 and 2.3 ± 1.6 in POST block2, which was 48% of the PRE value followed by a recovery of the pain ratings to 2.6 ± 1.1 in POST block3, 3.4 ± 0.8 in POST block4 and 4.2 ± 0.4 in the REC block. For the lower clonidine dose pain ratings decreased from 4.2 ± 0.8 in the PRE block to 4.2 ± 0.9 in POST block1 and 2.3 ± 1.4 in POST block2, which was 53% of the PRE value. Again, there was a recovery of the pain ratings to 3.2 ± 1.1 in POST block3, 3.6 ± 0.5 in POST block4 and 4.7 ± 1.6 in the REC block. Although reductions of pain ratings generally corresponded well to the reduction of SII dipole strength, but the time course of pain ratings failed to indicate a prolonged action of the higher clonidine dose. Further statistical analysis substantiated these findings. The results of the ANOVA (Table 2) yielded significant block effects, for both the dipole strength ($F = 8.7$; $p < 0.05$) and pain ratings ($F = 7.2$; $p < 0.05$), but no main or interaction effects occurred with dose on dipole strength or pain ratings. Subsequent t-test analysis of significant ANOVA effects is displayed in Table 3. When compared with the pre-Block significant reductions of SII-dipole strength (Table 3A) and pain ratings (Table 3B) occurred for both clonidine doses in POST blocks 2, 3 and 4. The failure of change in post Block 1 is in agreement with the pharmacokinetics of clonidine (Bischoff et al., 2000). The half maximum value of clonidine serum concentration is not reached before 10 min. No correlations were found between dipole strengths (Q) and pain ratings (Table 3C) with the one exception, subject KU.

Further analysis of the subjective effects of clonidine revealed an enhancement of tiredness and passiveness during maximal clonidine concentration (Fig. 5). During baseline the subjects rated their tiredness as 24.5 ± 18.1. Sixty minutes after medication the tiredness was enhanced to 63.3 ± 34.3 (258% of start value) which lasted until 120 min after clonidine administration with
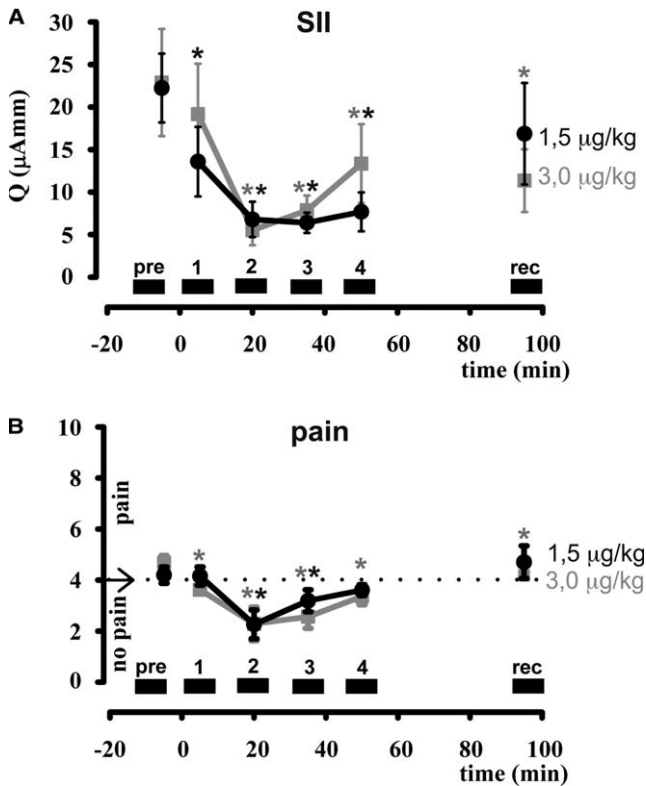
Fig. 4. Mean dipole strength values (A) and the pain ratings (B) with standard error of the mean over all subjects. The dipole was fixed in the individual SII area for each subject (see Fig. 2). It is shown, that SII-activity and the pain ratings are attenuated after clonidine application.

Table 2
Results of the ANOVA for the dipole strength (A) and pain ratings (B)

	df	F	p	p[ε]
A. Dipole strength				
Block	5	8.868	<0.001	0.008
Concentration	1	0.033	0.297	0.609
B. Pain rating				
Block	5	7.244	<0.001	0.026
Concentration	1	0.318	0.597	0.597

A significant block effect ($p < 0.001$) with Greenhouse–Geisser-correction ($p[\varepsilon] < 0.008$) for the dipole strength and the pain ratings ($p < 0.001$; $p[\varepsilon] < 0.026$) was found. No significant effect for concentration was found either for the dipole strength ($p = 0.609$) nor for the pain ratings ($p = 0.597$).

the value of 51.5 ± 22.8. The passiveness was rated as 38.7 ± 23.8 before clonidine administration and changed to 59.3 ± 28.3 after 60 min (152.3% of the PRE value) and 51.5 ± 30.7 after 120 min. Before low dose clonidine administration the subjects rated their tiredness as 37.1 ± 32.5. After 60 min the tiredness was enhanced to 64.5 ± 24.9 (171% of PRE value) which recovered after 120 min to values of 32.2 ± 27.7. The passiveness was rated as 33.0 ± 22.0 before clonidine administration and changed to 50.8 ± 32.2 after 60 min (153.4% of the PRE value) and 32.5 ± 23.5 after 120 min.

Table 3
Results of the *t*-tests for the dipole strength (A) and the pain ratings (B)

	1.5 μg/kg Clonidine		3.0 μg/kg Clonidine	
	t-Value	*p*-Value	*t*-Value	*p*-Value
A. Dipole strength				
Pre-post 1	2.69	0.021	1.17	0.147
Pre-post 2	2.83	0.018	3.19	0.012
Pre-post 3	4.72	0.002	3.03	0.015
Pre-post 4	3.81	0.006	2.21	0.039
Pre-rec	1.09	0.161	2.86	0.018
B. Pain rating				
Pre-post 1	0.14	0.445	3.44	0.009
Pre-post 2	2.75	0.02	2.70	0.022
Pre-post 3	1.86	0.061	3.47	0.009
Pre-post 4	1.42	0.107	3.22	0.011
Pre-rec	−1.02	0.178	1.68	0.076
	r-Value	*p*-Value	*n*-Value	
C. Correlation				
HE ($Q * PR$)	0.453	0.139	12	
KU ($Q * PR$)	0.942	<0.001	12	
ME ($Q * PR$)	0.499	0.099	12	
PR ($Q * PR$)	0.24	0.524	12	
SA ($Q * PR$)	0.361	0.248	12	
WA ($Q * PR$)	0.46	0.886	12	

Clonidine reduces the SII-dipole strength and the pain ratings. A correlation (*C*) between the dipole strength (*Q*) and the pain rating (PR) for the single subjects was only found for subject KU.

4. Discussion

By using an experimental pain model in six healthy volunteers in combination with MEG measurements this study demonstrates a substantial reduction of pain intensity in parallel with decreased evoked activity in the secondary somatosensory cortex (SII) following administration of clonidine, at doses of 1.5 and 3.0 μg/kg body weight. Dipole reconstruction based on the individual brain morphology localized the induced magnetic activity maximum within a latency range from 90 to 120 ms reliably within the SII cortex in all subjects. The intraindividual redetection accuracy was below 6 mm, which is the spatial resolution limit of our measurements and calculations. Although both subjective and physiological parameters of pain decreased after clonidine they were not statistically correlated. This supports the idea that stimulus induced SII activity does not necessarily reflect the painfulness of stimulation. Furthermore, we could not find any differences according to the two doses of clonidin, which could indicate a ceiling effect on SII activity. Using the lower dose of 1.5 μg/kg, the SII activity was already reduced to a minimum value near the level of background noise as early as after 20 min post medication, from which no further reduction is possible. On the other hand the time course of changes suggests a longer reduction of pain-induced SII activity for the higher compared to the lower
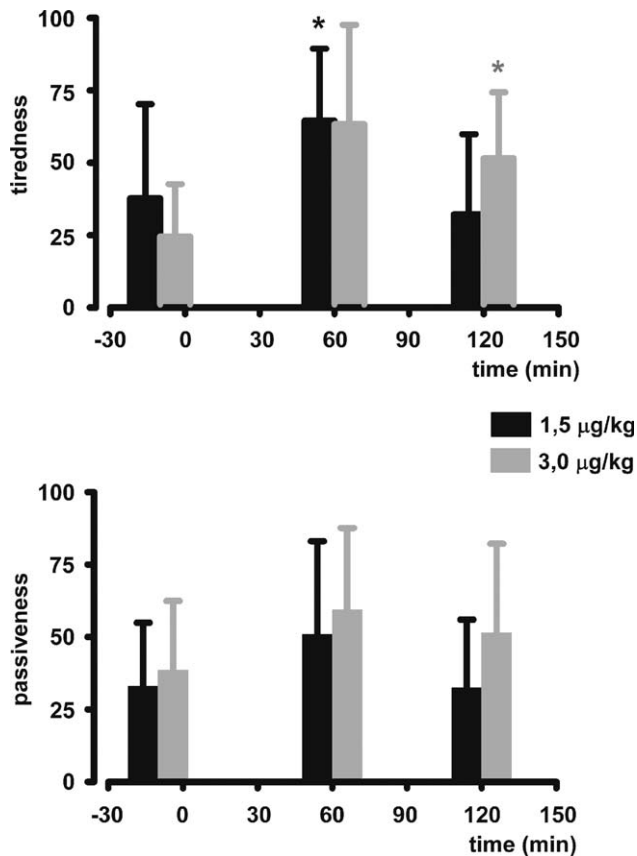
Fig. 5. Results of the questionaire dealing with the individual feeling of tiredness (above) and passiveness (below) of all subjects, 10 min before the experiment and 60 and 120 min after it.

clonidine dose, compatible with the pharmakokinetics of clonidine and findings of other authors (Bischoff et al., 2000, 2004).

Pain was induced by brief electrical current pulses, which were applied intracutaneously by a tiny hole through the horny layer of the middle fingertip, thus delivering the stimulus in the nearest neighbourhood of cutaneous nociceptors. This model induces a distinct pinprick pain and has shown its usefulness in many experiments measuring pain and pain relief under efficient analgesics (for review see Bromm and Lorenz, 1998). But all experimental pain models co-activate receptors of the tactile system as well, maybe also the infrared laser heat pulse (Treede et al., 1995). There is no doubt that tactile information reaches primary and secondary somatosensory areas. Therefore experimental pain-inducing stimuli always activate the SII cortex to a higher or lower degree, as well as non-nociceptive afferents, thus activation of SII is not necessarily a sign for pain experience (for a detailed discussion see Bromm et al., 2000).

Earlier studies of our group demonstrated the effects of habituation and morphine on subjective pain and pain evoked SII activity using the same intracutaneous pain model in a placebo-controlled design (Quante

et al., 2004). Given these results that yielded only small placebo effects the investigated decrease of pain evoked activity during the present study is likely due to the administration of clonidine even though we decided not to involve a placebo control in this study for procedural reasons.

The observed reduction of experimental pain in this study is consistent with clinical reports. Although placebo experiments are necessary to document new properties of drugs, and would have complemented our findings for the purpose of this study, pre-post comparisons seemed sufficient. Furthermore these experiments are extremely expensive and the mean values and normative variances of dipole identifications in SII are well known within and between subjects from a huge number of preceding experiments using the same standardized design (Lorenz et al., 2005; Nakamura et al., 2002; Bromm, 2001). However, the effects due to the long session duration are in the order of 5–8%. Because of this, it is clear that clonidine in both concentrations attenuates the SII activity drastically by 50% or more. Thus, the question is how clonidine interacts so strongly with pain perception. For example, in postoperative pain management intrathecal application of clonidine is used successfully to reduce the dose of morphine (Eisenach et al., 2000; Kanui et al., 1993; for review see Bischoff and Kochs, 1993). Studies in animals and patients have shown that the transdermal, epidural and intravenous administration of clonidine reduces pain intensity in neuropathic pain syndromes for periods varying from some hours up to 1 month. However, there is little evidence for a specific antinociceptive effect of intravenous administered clonidine (Bernard et al., 1995; Eisenach et al., 1998; Hao et al., 1996). These authors conclude that the clonidine-related decrease in pain experience depends on the level of arousal and is most probably not due to direct actions on the nociceptive system (see also Kakigi et al., 1996; Hämäläinen et al., 2000; Höchstetter et al., 2000; Nakamura et al., 2002). On the other hand, it is well known that SII activity depends on the vigilance level and on attentional states of the subject under investigation (Mima et al., 1998; Sarter et al., 2001; Nakamura et al., 2002). Obviously the SII cortex is tonically pre-primed by subcortical regions, which control the state of vigilance and arousal. Sedatives, tranquilizers and hypnotics attenuate stimulus evoked SII activity as well as mental distraction from the stimulus event. Also clonidine is well known to reduce vigilance and arousal (Bischoff and Kochs, 1993; Coull et al., 1995; Clark et al., 1986). Analysis of the spontaneous electroencephalogram (EEG) supports these observations. Clonidine attenuates the alpha rhythm and increases slow theta and delta rhythms (Bischoff et al., 2000), parameters that are well known to correlate with reaction time and subjective fatigue. A limitation of our study is that we only evaluated sub-

jective perceptions like tiredness and passiveness without raising reaction times or other clinical parameters of sedation and directly relate this to the action of clonidine on the SII cortex. For this reason we cannot clearly differentiate between specific and unspecific modulations of pain induced SII activity, a question that need to be addressed in further studies with greater focus on multi-modal assessment of sedation in comparison with MEG and EEG. Nevertheless, we were able to show, that clonidine decreases pain ratings and pain evoked SII activity allowing the conclusion that intravenous clonidine, and not only intrathecal clonidine, is able to relieve pain, but the detailed cortical mechanisms of intravenous clonidine on the pain system remains unclear.

5. Conclusions

Intravenous administration of clonidine was able to reduce pain evoked SII activity (decrease from PRE = 100% to POST2 = 22%) and pain ratings (decrease from PRE = 100% to POST2 = 48%), without significant correlation between these parameters. Similarly an increase of tiredness (258%) and passiveness (152.3%) was observed. Therefore, not only the intrathecal, but also the intravenous application of clonidine suppresses pain. Given the close association of pain perception and vigilance, the observed attenuation of pain evoked responses, represented at the level of the SII cortex, can be explained by a reduction of vigilance and arousal, effects of clonidine that have been reported earlier and something for which clonidine is well known. Further studies using physiological indicators of sedation in combination with those of pain can better discriminate the relative contribution of unspecific sedative and specific analgesic clonidine actions.

Acknowledgements

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