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The influence of music and music therapy on pain-induced neuronal oscillations measured by magnetencephalography

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Modern forms of music therapy are clinically established for various therapeutic or rehabilitative goals, especially in the treatment of chronic pain. However, little is known about the neuronal mechanisms that underlie pain modulation by music. Therefore, we attempted to characterize the effects of music therapy on pain perception by comparing the effects of 2 different therapeutic concepts, referred to as receptive and entrainment methods, on cortical activity recorded by magnetencephalography in combination with laser heat pain. Listening to preferred music within the receptive method yielded a significant reduction of pain ratings associated with a significant power reduction of delta-band activity in the cingulate gyrus, which suggests that participants displaced their focus of attention away from the pain stimulus. On the other hand, listening to self-composed "pain music" and "healing music" within the entrainment method exerted major effects on gamma-band activity in primary and secondary somatosensory cortices. Pain music, in contrast to healing music, increased pain ratings in parallel with an increase in gamma-band activity in somatosensory brain structures. In conclusion, our data suggest that the 2 music therapy approaches operationalized in this study seem to modulate pain perception through at least 2 different mechanisms, involving changes of activity in the delta and gamma bands at different stages of the pain processing system.

1. Introduction

Pain is an unpleasant feeling that can be influenced by various psychological and contextual factors. Different methods in psychotherapy target emotional modulations to promote pain relief or strengthen the capacity to cope with pain. An interesting approach is the integration of music. The use of music for healing has been known throughout the history of medicine in many cultures. The oldest testimonies can be dated back to the fourth millennium BC in the Egyptian culture [24], but the best-known report might be found in the Old Testament about King Saul's convalescence from depression with the help of David playing the harp. Further sources from the Greek, Roman, Arabian, and shamanistic healing procedures document music as therapy for various therapeutic or rehabilitative goals [9,29]. Notably, different music styles or harmonic patterns are capable of generating quite different mood states [18], depending on individual experiences with music, memories, and personal preferences for certain music styles. Music is considered to recruit neural circuits similar to those previously associated with emotional states [3]. Despite numerous clinical reports of benefits of music in management of different pain conditions [5,7,26,27], the underlying neuronal mechanisms are widely unknown. Neuroimaging studies have revealed anatomical pathways involved in the modulation of pain by distraction or higher-order cognitive processes, the latter involving phenomena such as placebo-induced analgesia [2], perceived control over pain [35], or religious beliefs [36].

In this study we used repetitive painful laser stimuli that reliably activate pain-relevant brain structures as revealed by both electroencephalography (EEG) and magnetencephalography (MEG) [21]. The design of our study aimed to conceptualize important features of 2 different concepts of music therapy within an experimental pain paradigm. First, the so-called receptive music therapy [31] uses preferred music to promote associations of well-being opposing the pain. Second, we used a method referred to as entrainment [8], which involves active participation of patients in composing and performing music together with a

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therapist. Pain reduction in the receptive method is assumed to be primarily mediated by distraction. In contrast, within the entrainment method, the use of self-composed music with opposing valences of pain and healing music requires an intense interaction between music therapist and participant on promoting the capability of actively controlling the pain. Distraction, which we assume to mainly inhibit pain by the receptive approach, has been found to reduce the amplitude of late laser-evoked potential (LEP) components generated in the cingulate cortex [19]. We hypothesize that laser-evoked activity in the delta band that mainly contributes to the late LEP component should correlate with pain under the influence of the receptive method. No study thus far has examined the effects of active coping on pain-evoked potentials or MEG fields. However, it is conceivable that the clear difference of attentional engagement away or toward the pain between the 2 approaches of music therapy might influence pain perception differently and accordingly differ with respect to neuronal oscillations within the described pain matrix.

2. Materials and methods

2.1. Participants

Before the start of the experiment, the protocol was approved by the local ethics review board. Twenty right-handed participants (10 female, age 27.2 ± 4 years) were involved in this study after they provided written informed consent. All participants were tested for the absence of normal hearing and were free to terminate the experiment at any time. Additionally all participants were interviewed for musicality, whether they regularly listen to music or play any instrument. Only 1 participant played an instrument professionally.

2.2. Music therapy

The entrainment music therapy method involves a defined procedure consisting of 4 phases: (1) an extensive pain interview with indication for treatment and formulation of the therapeutic contract; (2) the composition of a so-called "pain music" and "healing music" with the help of a variable set of instruments that are provided; (3) the application phase, in which the therapist plays the individually composed music for the patient; and (4) the reflective discussion of the previous phases. For further information on the procedure and an explanatory approach see Metzner [20].

In our experiment, the pain and healing music were individually composed specifically for the experimental laser pain, which was applied to the participants before the composition procedure (see also experimental protocol). During the composition procedure, the participants composed their pain music and healing music together with the music therapist in a specially designed music therapy room, which was equipped with different instruments such as flutes, guitar, piano, cello, and various percussion instruments. Either the participants picked the instruments by themselves or the music therapist chose the instruments according to the sound the participants had in mind reflecting the laser pain or healing music. Then these sounds and musical pieces were played together and composed with the music therapist separately for the pain music and the healing music. When the music met the participants expectations as pain music and healing music, the composition was digitally recorded for the main MEG experiment. For the receptive music therapy, subjects were asked before the experiment to provide their favourite music, which usually induces well being, on CD or an MP3 stick.

2.3. Music stimuli

The digitized music was cut into 1-min epochs and normalized for overall spectral power; to avoid systematic differences in physical properties of music, we applied a normalization procedure. The intensities of the sounds were adjusted by equalizing the root mean square power across all sound files. To avoid onset and offset clicking transients, the sound files were windowed with a linear 10-ms rise and fall time. An ANOVA of the Fast Fourier transformed music did not show any differences in volume or spectral power in different frequency bands across the resulting normalized epochs. In a nonstatistic descriptive manner, the music varied between the participants and between individual pain and healing music. In general, the pain music can be best described as comprising sharp high-pitch sounds, whereas the healing music consisted of warm and calming motifs (see Supplementary Audio Files online). During the experiment, the music was presented at 60 dB using a custom-built MEG-compatible auditory earphone device (Stax SRM-212 Driver Unit and Stax SR-003 electrostatic transducers, Stax Limited, Miyoshi (Saitama Prefecture), Japan), which was connected via plastic tubes to the participants' ear. For control conditions, healing and pain music of 1 other participant as well as a no music condition were presented during the experiment. Hence, each participant was exposed to his or her own healing music, his or her own pain music, his or her own preferred music, alien pain music, alien healing music, and no music during the experiment (Fig. 1).

2.4. Physiological data and reaction times

Before the MEG experiment, the influence of music was tested for different arousal and attention parameters. Heart rate, skin conductance, body temperature, and breathing rate were acquired during listening to the 5 different music conditions using a Biopac MP35 device (Biopac Systems, Inc., Goleta, CA). Furthermore, a reaction time task was performed while listening to the music. The participant had to fixate a cross and press a button as fast as possible when the fixation cross changed to a cycle symbol. Visual stimuli and music were controlled and presented on the computer screen using Presentation software (Neurobehavioral Systems, Albany, CA).

2.5. Pain stimuli

We delivered brief infrared laser stimuli of 1-ms duration and a beam diameter of 5 mm to the dorsum of the left hand using a thulium laser (wavelength 2 μm, StarMedTec, Starnberg, Germany). Individual pain thresholds were determined using 3 series of increasing and decreasing stimuli. Beginning at 160 mJ, we used a step size of 20 mJ. The procedure of determining individual pain threshold was important to make the test participants familiar with the laser stimuli and instruct them to clearly distinguish between nonpainful and painful laser stimuli. Pain was defined as a light pin prick or burning sensation. During the experiment, 2 different intensities were used that were clearly in the painful range of all participants, a laser energy of 450 mJ for the low pain stimuli and 600 mJ for the high pain stimuli. Studies examining the effects of analgesic drugs on pain-evoked potentials proved the use of 2 different stimulus intensity within a randomized series to minimize habituation effects [4]. The participants rated the laser pain stimulus intensity and unpleasantness by filling up the x and y scale of a coordinate system using a joystick with their right hand (Fig. 1). Thus, the participants were able to rate sensory discriminative and affective motivational components of pain within 1 joystick move. The individual rating was displayed online on a screen using a square within the coordinate system, which changed size and colour depending on the strength of the intensity rating (labeled as painful, from pale red to dark red) and the unpleasantness rating (labeled as unpleasant, from pale blue to dark blue). Hence, a maximal unpleasant and painful pain rating was displayed with a violet square of maximal size (Fig. 1C).

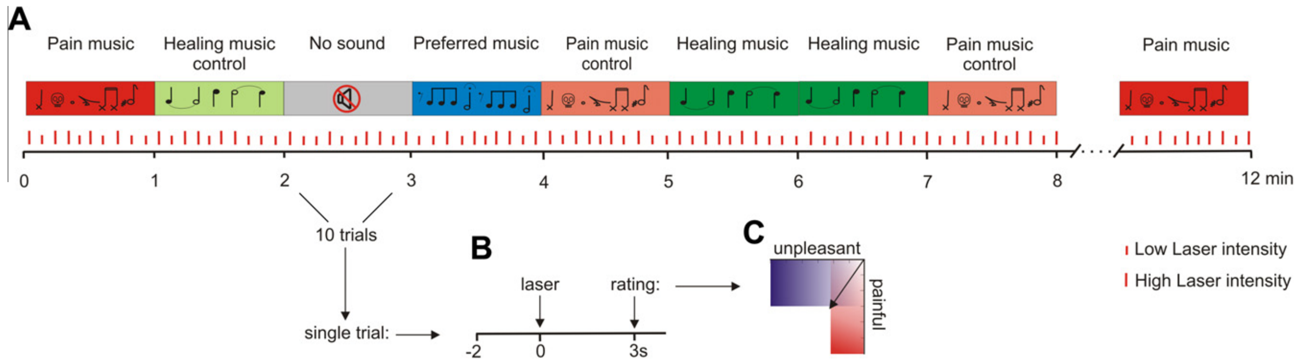

Fig. 1. Experimental protocol and sequence of stimulus conditions. (A) Schematic of 1 of 4 blocks comprising 5 different music listening conditions and silence, each with a 1-min duration and 10 laser trials. (B) Each trial began with a fixation cross on the screen 2 s before the pain stimulation. Three seconds after the laser stimulus, a visual coordinate system was displayed that prompted the participant to rate the pain. (C) The participants had to rate stimulus intensity and unpleasantness by adjusting values on the x axis and y axis of the visual coordinate system using a joystick with their right hand. The displayed rectangle changed height, length, and colour accordingly. A stimulus perceived more unpleasant than painful yielded a blueish rectangle with more expansion on the x axis.

2.6. Experimental protocol

Two experimental days were scheduled for all participants. During the first day, the pain thresholds were determined and the participant was familiarized with the pain sensation induced by the laser stimulus. On the same day, the extensive interview with the music therapist was conducted on the participants' musicality and musical practice and on the laser-stimulated pain experience, followed by the composition and recording of the pain and healing music. During the second experimental day, physiological data (heart rate, skin resistance, body temperature, breathing rate) and reaction times were collected before the MEG measurements. During the MEG experiment, participants were comfortably seated in an electromagnetically shielded chamber with their eyes directed at a fixation cross. The experiment consisted of 4 blocks in total, comprising 80 pain stimuli trials (50% with low pain intensity, presented randomly) per block. During the experiment, the participants were exposed to the different types of music, which changed every minute, after 10 laser stimuli (Fig. 1A). To avoid systematic errors due to habituation effects, the different music epochs were played in a randomized order for the first half of the block and then mirrored for the second block half. Each trial began with appearance of the fixation cross on the screen. After 2 s the laser pulse was delivered, followed by display of a coordinate system on the screen 3 s later (Fig. 1C). After each block, the randomization for the laser energy and the music epochs was repeated.

2.7. Acquisition and analysis of MEG data

MEG was recorded using a 275-channel whole-head system (CTFMEG, Coquitlam, BC, Canada) in a magnetically shielded room. The electro-oculogram was recorded simultaneously for offline artifact rejection. Head position relative to the MEG sensors was measured before and after each recording block. For all analyzed data sets, head displacements were below 5 mm. MEG signals were low-pass filtered online (cutoff 400 Hz) and sampled at 1200 Hz. Trials containing muscle artifacts or signal jumps were rejected offline from further analysis using semiautomatic procedures. Eye blinks and eye movements were rejected manually by visual inspection. Line noise removal (50 Hz in Europe) was performed by selecting data segments of 10-s length with the epochs of interest in the center. These segments were Fourier transformed, and the 50-, 100-, 150-, and 200-Hz components of the spectra were zeroed. Subsequently, the time courses were reconstructed by inverse Fourier transformation and epochs of interest were cut out of these denoised 10-s data segments. T1-weighted structural magnetic resonance images (MRIs) were recorded for all participants on a third day. For source reconstruction, individual single-shell models [25] were derived from the segmentation of these structural MRIs. MEG data were analyzed offline using the open-source software toolbox Fieldtrip (www.ru.nl/fcdonders/fieldtrip) running under Matlab (The Mathworks, Natick, MA).

2.8. Statistical analysis

For statistical analysis, SPSS 10.0 was used (SPSS, Chicago, IL). All parameters were first checked with a 1-sample Kolmogorov–Smirnov test for normal distribution. Pain ratings and MEG sensor data were analysed using a 1-way factorial repeated-measures analysis of variance (ANOVA) testing effects of music. Furthermore, a 2×2 ANOVA was applied to test effects of the factors music and self-relation. Significant main and interaction effects were followed by post hoc paired *t* tests.

2.9. Spectral analysis of sensor data

Frequencies up to 10 Hz were analyzed using a sliding Hanning-window Fourier transformation with a window length of 500 ms and a step size of 20 ms. Spectral analysis of MEG data above 10 Hz was performed using a sliding-window multitaper analysis [22]. In short, the data were multiplied by $N > 1$ orthogonal tapers and Fourier transformed, and the N spectral estimates were averaged. In case of power estimation, the spectra for each individual taper were magnitude squared after Fourier transformation. As data tapers, we used the leading 2TW-1 prolate spheroidal (slepian) sequences, in which T denotes the length of the tapers and W the half bandwidth. These tapers optimally concentrate the spectral energy of the signal over the desired half bandwidth W. Averaging across trials was finally performed in the frequency domain. A window of 300-ms length was shifted over the data with a step size of 20 ms. Spectral smoothing of 10 Hz was achieved by 5 slepian tapers.

2.10. Source reconstruction

To estimate the spectral amplitude of responses at the cortical source level, we used the adaptive spatial filtering technique of linear beamforming [13,33], as described previously [28]. In short, for each time frequency of interest and source location, a linear filter was computed that passed activity from that location with unit gain while maximally suppressing activity from other sources. All source-level analyses were independently performed for 3 frequency bands, which showed pain-induced modulations on the sensor level: 2 to 6 Hz and 300 ms, 24 to 34 Hz and 1100 ms, and 70 to 80 Hz and 350 ms. For each recording session, forward models were computed using individual single-shell volume conductor models and the measured head positions. Whole-brain source reconstructions were performed on a regular 3-dimensional grid of 7 mm resolution and linearly interpolated to 1 mm resolution. The individual sources underwent relative baseline correction using, for each voxel, the power of the neural activity in the same frequency range at time point −500 ms and expressing the response as a z-score. For the correlation analysis, baseline-corrected responses for each block were correlated with the mean subjective pain ratings during the respective type of music. The resulting correlation coefficients were quantified as z-scores and statistically tested against a zero distribution. The resulting *P* values were used to mask nonsignificant results. Thus, only statistically significant correlations were superimposed as z-scores to the standard MRI. All results were corrected for multiple comparisons by using the false discovery rate [1]. MNI (Montreal Neurological Institute) coordinates of significant voxels were transformed to Talairach coordinates [30] to determine locations using the Talairach Daemon (http://ric.uthscsa.edu/resources).

3. Results

3.1. Effects of music on physiological data and reaction times

Before the MEG experiment, the influence of music types on different biopsychological parameters was tested. Heart rate, skin resistance, body temperature, and breathing rate were acquired during listening to individual pain, healing, and preferred music and for alien pain and healing music. First, an ANOVA was used to estimate the influence of music on heart rate, body temperature, skin resistance, breathing rate, and reaction times. The music type had no significant influence on the heart rate ($F_{(4)} = 1.8$, $P = .17$), skin resistance ($F_{(4)} = 1.7$, $P = .17$), body temperature ($F_{(4)} = 1.5$, $P = .2$), or breathing rate ($F_{(4)} = 1.7$, $P = .2$). However, a significant main effect for the reaction times ($F_{(4)} = 2.7$, $P = .038$) was found. Further post hoc *t* tests revealed a significant difference of reaction time between personal pain and healing music ($t = 2.5$, $P = .02$), but not between the alien types of music. Reaction times were significantly faster for healing music (mean = 294 ms ± 19) compared with pain music (mean = 344 ms ± 34).

3.2. Modulation of pain ratings by listening to music

Listening to music had a significant influence on ratings of pain intensity and evaluation of unpleasantness (Fig. 2). To increase the number of trials for the statistical analysis of the different music conditions, high and low laser stimulations were pooled. The highest pain ratings were observed during listening to the self-related pain music followed by self-related healing music and preferred music. The significance of this effect was stronger for the unpleasantness ratings (Fig. 2B) compared with the intensity ratings (Fig. 2A), which indicates that the affective aspects of pain processing are more strongly influenced by individual pain, healing, and preferred music compared with the sensory aspects of pain processing. The 1-way ANOVA revealed a main effect for music on the unpleasantness ratings ($F_{(5)} = 7.9$, $P < .001$) and the intensity ratings ($F_{(5)} = 3.7$, $P < .01$). Furthermore, to test the influence of self-related music, a 2 × 2 ANOVA was calculated with the factors music (pain or healing) and self-relation (composed by the participant or the control participant). For the unpleasantness ratings, a significant main effect for music was found ($F_{(1)} = 6.9$, $P < .05$) and a significant interaction between music and self-relation ($F_{(1)} = 5.8$,

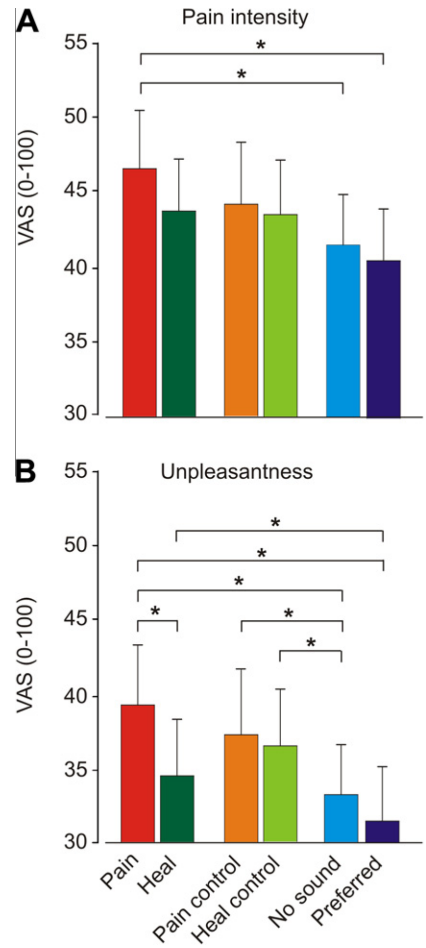

Fig. 2. Pain ratings. Listening to music had a significant influence on pain perception for the intensity (A) and unpleasantness (B) ratings. The highest pain ratings were observed during listening to the self-composed pain music, followed by self-composed healing music; listening to preferred music resulted in the lowest pain ratings. This effect was even stronger for the unpleasantness ratings. The control condition was pain and healing music composed by other participants. No sound also yielded lower pain and unpleasantness ratings than the other conditions except healing and preferred music. Significant differences ($P < .05$) are indicated by an asterisk.

$P < .05$) was observed. Regarding the intensity ratings, no significant effect or interaction was found. Thus the weaker effects of music on intensity ratings in comparison with unpleasantness ratings as revealed by the 1-way ANOVA involving all music types were obviously dependent on the preferred music condition. Intensity ratings fell below statistical thresholds of significance when only the composed music types were analyzed. Further *t* tests revealed higher unpleasantness ratings during pain music compared with both healing music ($t = 2.9$, $P < .01$) and preferred music ($t = 5.1$, $P < .001$), as well as higher unpleasantness ratings during healing music compared with preferred music ($t = 2.8$, $P < .05$). Pain intensity ratings were significantly higher during pain music compared with preferred music ($t = 3.2$, $P < .01$), as well as during healing compared with preferred music ($t = 3.7$, $P < .05$). Additionally, unpleasantness ratings were higher both during pain music ($t = 2.3$, $P < .05$) and during healing music compared with no sound ($t = 2.5$, $P < .05$). Marginal significance of higher unpleasantness ratings appeared when comparing self-composed pain music and the control pain music ($t = 1.9$, $P = .075$), a trend that was similarly observed for the intensity ratings ($t = 2.0$, $P = .066$). To compare all music conditions with no sound, subsequent *t* tests were performed. For the intensity ratings, only self-composed pain music was different from the no sound condition ($t = 2.5$, $P < .05$). The same was true for the unpleasantness ratings of self-composed pain music when compared with the no sound condition ($t = 3.6$, $P < .01$).

In summary, both music stimuli of the receptive and the entrainment methods induced a modulation of affective and sensory pain in a complex manner. The music stimuli of the receptive method did not significantly alter pain perception compared with the no-sound condition, but were significantly lower when compared with the music stimuli of the entrainment method. However, although the music stimuli of the entrainment method yielded a generally higher level of pain, there was a substantial difference in perceived pain and unpleasantness dependent on the valence of personally relevant self-composed pain or healing music.

3.3. Neuronal oscillations after painful stimulation

The grand mean time-frequency analysis of the MEG data revealed 3 patterns of pain-induced changes in oscillations after laser stimulation (Fig. 3). In the time range from 200 to 500 ms, an increase in the delta band (maximum 3 Hz, 300 ms) appeared, which was most prominent at the central and parietal sensors (Fig. 3C). This component was accompanied by an increase in gamma power with latencies from 250 to 400 ms (maximum 75 Hz, 350 ms) and with maximal occurrence at central sensors (Fig. 3A). Furthermore, a decrease in the beta band with latencies from 300 to 1500 ms (maximum 28 Hz, 1100 ms) was prominent at temporal sensors.

These 3 components were modulated to different degrees in the tested music conditions (Fig. 4). According to our a priori hypotheses, we tested the effects of the stimuli used by receptive music therapy by a 1-way ANOVA involving no sound and preferred music conditions. It yielded a significant difference ($F_{(1)} = 21.8$, $P < .01$) with less delta-band power during preferred music compared with no sound ($T_{(18)} = -3.2$, $P < .01$) (Fig. 4C). A 2-way (2×2) ANOVA with the factors music valence (pain or healing) and self-relation (self vs alien) revealed effects of the music stimuli use by the entrainment method. It showed significant main effects in the gamma band for both music valence ($F_{(1)} = 5.7$, $P < .05$) and self-relation ($F_{(1)} = 4.5$, $P < .05$), as well as a significant interaction between these factors ($F_{(1)} = 6.2$, $P < .05$). Direct t test comparison of composed music with the no sound conditions showed no significant difference. Hence, listening to pain music induced stronger oscillations in the gamma band compared with healing music when pain music had been self-composed ($t_{(1)} = 3.15$, $P < .01$) (Fig. 4A). No significant effects occurred for laser-induced beta-band changes (Fig. 4B).

In summary, the 2 approaches of music therapy yielded differential effects on delta-band and gamma-band activities induced by brief repetitive laser stimuli. Music stimuli using the receptive method, as tested by preferred music against no sound, led to a decrease in laser-induced delta activity during preferred music, whereas no effect in this frequency band occurred with music stimuli used by the entrainment method. In contrast, this latter approach, as tested by valence and self-relation of individually composed music, yielded a significant modulation of laser-induced gamma-band activity during self-composed healing music.

3.4. Cortical topography of pain-induced neuronal oscillations

This section describes the brain topographical distribution of frequency-specific MEG activity after laser stimuli. We estimated neural activity after pain stimulation at the cortical source level using a spatial filtering technique (linear beamforming; see Section 2). We separately investigated the 3 frequency bands that revealed stimulus-related changes in the time frequency representations (Fig. 5). In accordance with previous reports [17], the delta component (2 to 6 Hz, 300 ms) was localized in the contralateral somatosensory cortex and the cingulate gyrus (Fig. 5C). The desynchronisation in the beta band (24 to 34 Hz, 1100 ms) was located in bilateral sensory motor areas (Fig. 5B). This pattern of beta suppression is known to occur during tactile and pain

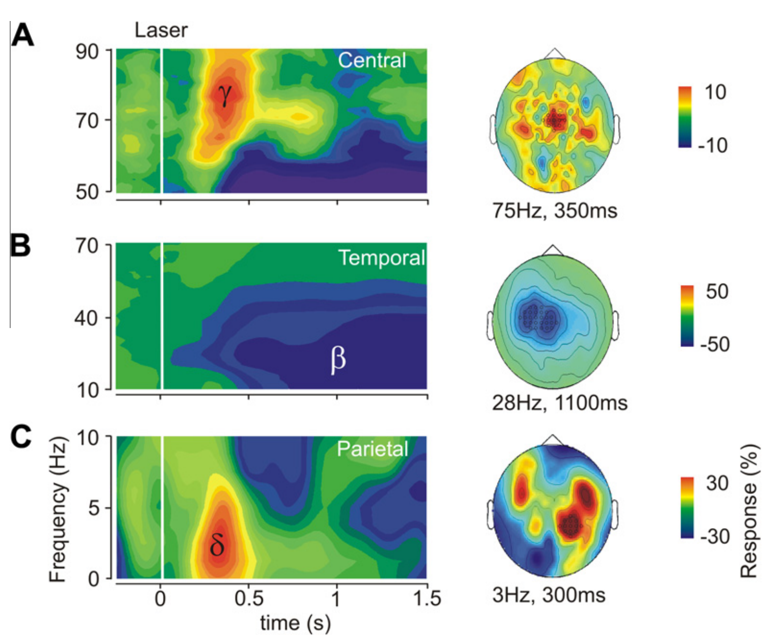

Fig. 3. Pain-induced oscillations after laser stimulation. The plots to the left show time-frequency representations of the pain-induced responses averaged across central (A), temporal (B), and parietal (C) cluster of sensors. Note that different frequencies are displayed in each plot. Responses are computed as percentage changes in signal amplitude relative to the baseline (500 ms before laser onset). Panels to the right show the topographic distribution of the response components. Three oscillatory response components were observed after laser stimulation. An increase in the delta band (maximum of 3 Hz at approximately 300 ms poststimulus) was most prominent at the central and parietal sensors. This component was accompanied by an increase in gamma power (maximum of 75 Hz at approximately 350 ms) with maximal strength at central sensors. Furthermore, a sustained decrease in the alpha and beta bands (maximum of 28 Hz at approximately 1100 ms) appeared at the bilateral temporal sensors.

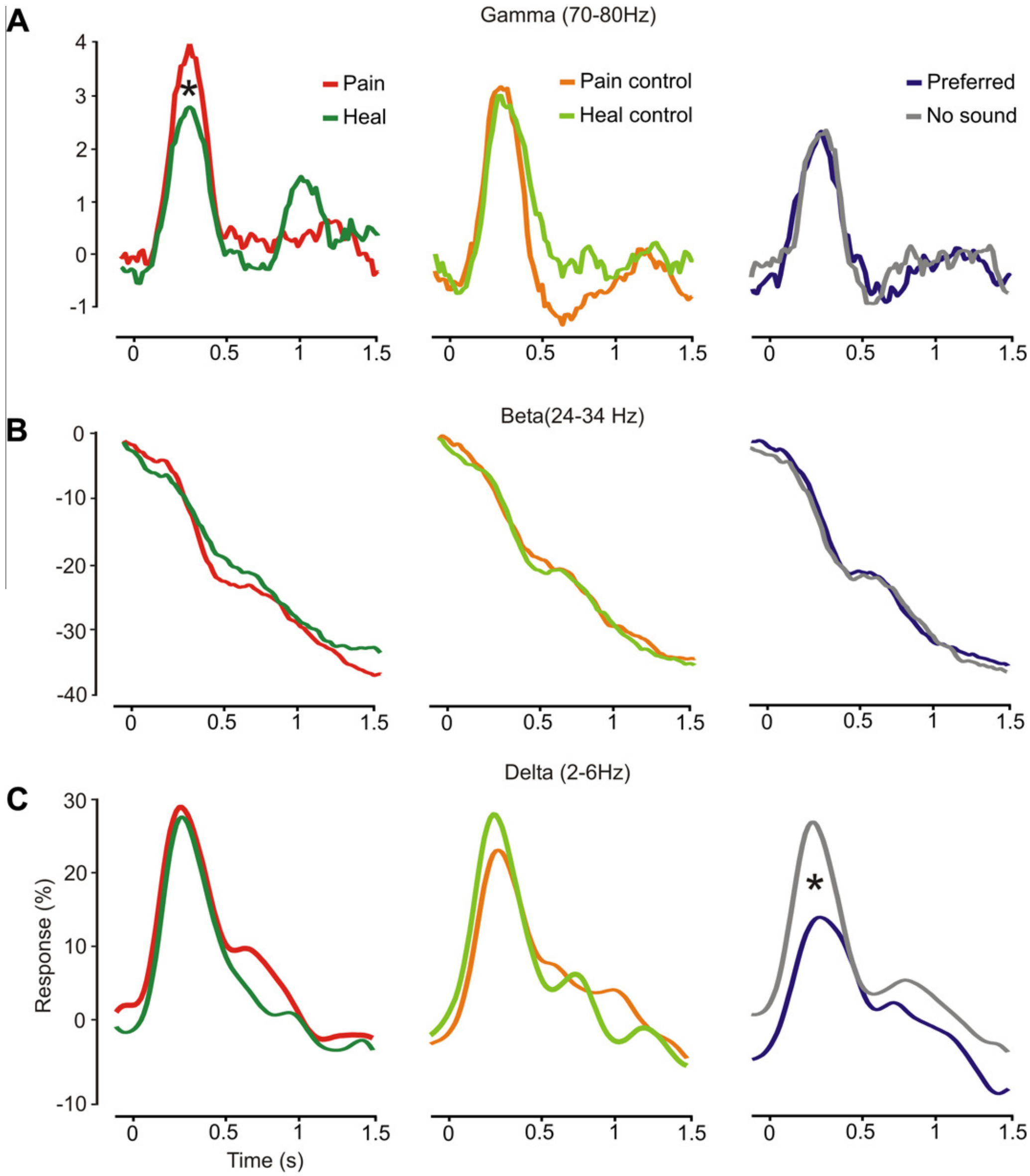

Fig. 4. Poststimulus time courses of grand mean responses within gamma (A), beta (B), and delta (C) bands during different music conditions, expressed as percent change in signal power relative to prestimulus baseline (−500 to 0 ms). Significantly lower gamma-band activity (70 to 80 Hz) appeared during self-composed healing compared with pain music (A). Gamma-band activity did not differ between no sound and preferred music. No significant effects were observed in the beta band (24 to 34 Hz) (B). Delta power (2 to 6 Hz) was significantly lower during preferred music compared with the no-sound condition around 300 ms, whereas no differences between self-composed pain vs healing music were observed in this frequency band (C).

stimulation [6] and may relate to the coupling between pain perception and preparation of behavioural responses. Furthermore, gamma oscillations were prominent in the contralateral primary somatosensory (SI) cortex and ipsilateral insula/SII cortex (Fig. 5A). This is in accordance with previous studies [14,32] that have reported an increase in pain-induced gamma oscillations with latencies of 200 ms and frequencies around 70 to 80 Hz in primary somatosensory cortex and around 300 ms in the SII cortex [16].

Next, we were interested to further examine the role of oscillatory activity for pain modulation within both music therapy methods. In the entrainment method, correlations were calculated for each participant and source-level response during self-composed pain and healing music with the individual mean intensity and unpleasantness pain ratings, separately for gamma power (Fig. 6). In the gamma band, we revealed a significant correlation between neural responses and both intensity and unpleasantness ratings in the SI cortex (Fig. 6A). In the receptive music therapy, significant correlations between neural responses in the delta band and intensity ratings were found in the contralateral insula and the midcingulate gyrus (Fig. 6B). In summary, the 2 approaches of music therapy yielded differential effects on delta- and gamma-band activities on the sensor level as mentioned earlier, and different cortical generators could be revealed by the correlation analysis. Music stimuli used by the entrainment method, as tested by valence and self-relation of individually composed music, yielded a significant correlation of gamma-band activity and both unpleasantness and intensity ratings in the primary somatosensory cortex. In contrast, with music stimuli used by the receptive method, as tested by preferred music against no sound, correlation between delta activity and unpleasantness ratings were localized in the midcingulate cortex, whereas correlation between intensity ratings and delta activity was localized in the contralateral insula.

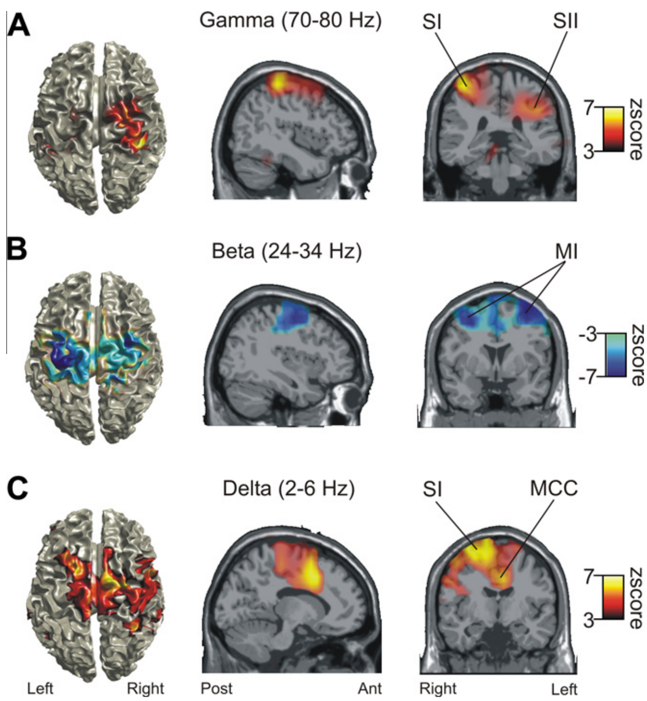

Fig. 5. Topographic source space maps of pain-induced activity in the gamma (A), beta (B), and delta (C) band at the cortical surface (left), sagittal (right), and coronal sections (middle) normalized to the Montreal Neurological Institute template brain. All functional maps display z-score distributions thresholded at $P < .05$ (corrected; random effects). Gamma-band activity (70 to 80 Hz, 350 ms) was prominent in the contralateral primary somatosensory cortex and ipsilateral insula/SII cortex. The decrease in the beta band (24 to 34 Hz, 1100 ms) was located in bilateral sensory motor areas (M1). The delta component (2 to 6 Hz, 300 ms) was localized in the centroparietal cortex including the contralateral somatosensory cortex (S1) and the midcingulate gyrus (MCC).

4. Discussion

In the present study, we aimed to characterize the cortical correlates of music therapy as a method to alter pain perception by using 275-sensor MEG in combination with laser-induced pain. Pain was manipulated by music stimuli of 2 different therapeutic approaches, receptive music therapy and the entrainment method. The receptive method involved participants choosing a favorite music to which they listened during repetitive painful laser stimuli in comparison with trial blocks in which no sound was presented. In contrast, with the entrainment method, pain and healing music were composed individually by the participants under supervision of a music therapist. A condition without any sound served as control. Psychophysical ratings yielded the highest pain and unpleasantness during music stimuli of the entrainment method compared with both receptive music and no sound condition. However, with the entrainment method, participants clearly rated pain unpleasantness and intensity lower for their own self-composed healing music compared with their own self-composed pain music, or compared with any music composed by other participants.

Before discussing the neurophysiological effects, we want to emphasize limitations regarding the interpretation of this psychophysical result. The use of painful laser stimuli within an experimental session using healthy volunteers does not directly compare the 2 music therapies regarding their efficacy in reducing clinical pain in patients. Instead, we attempted to operationalize, in an experimental laser pain model, major therapeutic features of the receptive and entrainment methods relating to distraction or active coping, respectively. Our main goal was to analyze putative differences in the neurophysiological effects on pain perception, but our results do not permit any direct conclusions regarding which of the 2 methods might be superior for pain management.

The experimental operationalizations of the 2 methods of music therapy that we used to manipulate laser pain yielded effects both in different frequency bands and in different brain structures. We regard this as evidence for different mechanisms by which different approaches of music therapy can alter pain processing.

The receptive method detaches the individual from pain, exploiting the personal preference for a certain music allowing emotional and attentional engagement with the musical stimulus. Although the comparison between receptive music stimuli with the no sound condition failed to reach a statistically significant reduction of pain intensity and unpleasantness, there was a significant power reduction of laser-induced delta-band activity in the MEG, localized in the midcingulate cortex and the anterior insula. This delta-band activity predominantly reflects late LEP components, which are known to be reduced in amplitude by distraction [19]. Thus, our data suggest that participants shifted their focus of attention from the pain stimuli to the music, which is consistent with numerous studies that have revealed reduced laser-evoked pain and brain potentials under the effect of distraction [19]. We consider global changes of alertness or arousal across conditions unlikely, as suggested by our physiological and behavioural data. The localization of delta activity within the cingulate cortex and the insula further agrees with the notion that both structures play an important role in the direction of attention toward pain [15].

In contrast, within the entrainment method, pain music and healing music being composed individually by the participants exerted major effects on laser-induced gamma-band activity in the SI cortex. Both the negative valence of pain music in contrast to the positive valence of healing music and the quality of the music as self-composed instead of composed by another person rendered the pain music most painful and unpleasant. Self-composed pain and healing music were associated with significant correlations between unpleasantness as well as intensity pain ratings and gamma-band activity in the somatosensory cortex. This suggests that the entrainment method involves modulation of pain perception at early cortical processing stages.

Gross et al. [14] showed that gamma oscillations in the SI cortex are particularly related to the subjective perception of pain. Using laser pain intensities near the individual pain threshold, they were able to show that participants' ratings of pain were stronger for laser stimuli that caused pain compared with the same stimuli when no pain was perceived. These findings indicate that gamma oscillations represent an important mechanism for processing behaviourally relevant sensory information [14] and that self-composed pain and healing music can modulate sensory input on early stages of pain processing. The enhancement of gamma band activity for pain compared with the healing music may provide a mechanism contributing to enhanced awareness for somatosensory signals from the stimulated body part.

An additional possibility is that enhanced gamma oscillations in the somatosensory cortex during pain compared with healing music could reflect a stronger coupling of SI activity with higher-order cortical processes. Gamma oscillations are linked to binding processes [10,11] and information transfer between cortical areas [12]. Synchrony in the gamma band may bias the routing of pain-related signals toward limbic structures, which are involved in emotional processing, monitoring, and descending control of pain [19]. Supporting this view, there is clear evidence that cortical gamma-band activity in response to pain stimuli can be strongly modulated by top-town influences such as attention [14,16].

Top-down modulation may be an important component of the entrainment method. During clinical sessions of the entrainment method, patients usually receive a combination of pain and healing music with a conscious pain experience related to a pathological

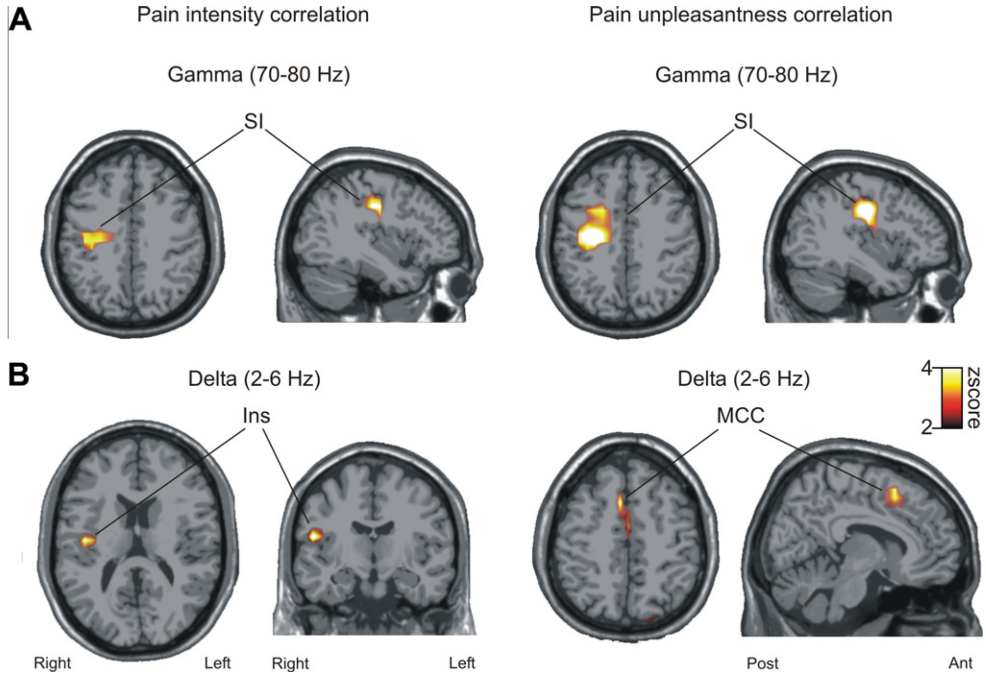

Fig. 6. Brain topographic maps of correlations between pain and unpleasantness ratings and delta- and gamma-band responses during preferred music, self-composed pain and healing music, and no sound. The subjective ratings, averaged over trials of 1 stimulus block, were correlated voxel by voxel with stimulus-induced delta- and gamma-band power, displayed as statistically significant z-score distribution on horizontal and sagittal planes of the standard MNI brain. (A) For the gamma-band and correlation within the self-composed pain and healing music, significant correlations were observed with both intensity and unpleasantness ratings in the contralateral primary somatosensory cortex (SI). (B) For the delta band, significant correlations between preferred music and no sound were observed in contralateral insula (Ins) for intensity ratings. Correlations between preferred music and no sound with unpleasantness ratings were found in the midcingulate gyrus (MCC).

condition. We hypothesize that the active manipulation of pain through the interactive steps of entrainment with the therapist facilitated participants to experience the pain as controllable. There is evidence that perceiving pain as controllable recruits prefrontal top-down mechanisms of pain modulation [23,34]. It seems likely that such top-down influences, mediating the focused attention toward the laser stimulus during the pain music condition, contribute to increased pain ratings and gamma oscillations in the somatosensory cortex.

The high attentional load associated with the entrainment method compared with the receptive method may also account for our finding that healing music did not yield significantly less gamma band activity than the no sound condition. The entrainment trials involved the simultaneous concentration on 2 sensory events, music and pain. Furthermore, they required subjects to match the pain stimuli with expectations or emotional significance according to associations they adopted in prior sessions of composing the music with a therapist. The no sound condition allowed subjects to be rather passive and to merely focus on delivering pain ratings.

In conclusion, our data suggest that the 2 music therapy approaches operationalized in this study seem to modulate pain perception through at least 2 different mechanisms involving changes of activity in the delta and gamma bands at different stages of the pain processing system. However, some limitations of our study should be emphasized. In our experiment, participants were presented with randomized 1-min pieces of music during pain perception, which is not comparable with the typical clinical situation, within neither entrainment nor receptive music therapy. In addition, the nature of very brief heat stimuli delivered by an infrared laser does not compare with long-lasting clinical pain, which has a fundamentally different impact. Nevertheless, using a controlled laboratory setting we were able to differentially manipulate important elements of music therapy leading to modulation of pain perception. Our results therefore contribute to a better understanding of the neurophysiological mechanisms that may render music therapy effective. Our study is consistent with the view that clinical settings of music therapy for pain management can exploit the capability of music to induce both relaxation and distraction, and can also offer creative tools and alternative ways for a therapist to interact with the patient, similar to cognitive-behavioral treatment, to help the patient actively explore and learn individual pain coping capabilities.

Conflict of interest statement

The authors have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2012.12.016.

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