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Spinal modulation of nociception by music

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Abstract

Numerous studies have demonstrated the capacity of music to modulate pain. However, the neurophysiological mechanisms responsible for this phenomenon remain unknown. In order to assess the involvement of descending modulatory mechanisms in the modulation of pain by music, we evaluated the effects of musical excerpts conveying different emotions (pleasant-stimulating, pleasant-relaxing, unpleasant-stimulating) on the spinally mediated nociceptive flexion reflex (or RIII), as well as on pain ratings and skin conductance responses. The RIII reflex and pain ratings were increased during the listening of unpleasant music compared with pleasant music, suggesting the involvement of descending pain-modulatory mechanisms in the effects of musical emotions on pain. There were no significant differences between the pleasant-stimulating and pleasant-relaxing musical condition, indicating that the arousal of music had little influence on pain processing.

1. Introduction

Music can make us smile or cry, dance or sleep (Sloboda and O'Neill, 2001), or even sometimes make us shiver with excitement (Blood and Zatorre, 2001). This is what makes music such an exquisite art form. The emotional power of music can also be harnessed in clinical settings to alleviate the unpleasant emotional states that usually accompany illness (Good et al., 2005). Although many studies have demonstrated the efficacy of music to reduce pain (Cepeda et al., 2006), the neuro-physiological mechanisms underlying the effects of music on pain still remain poorly understood.

In a previous study, we showed that the emotional valence of musical excerpts determines music-induced analgesia on acute heat pain in healthy individuals (Roy et al., 2008). Pleasant musical excerpts reduced pain, whereas unpleasant ones had no effects or tended to increase pain. These results are consistent with what has been observed with other emotional inducers, such as pictures (Meagher et al., 2001), films (Weisenberg et al., 1998), emotional sentences (Zelman et al., 1991), odours (Villemure et al., 2003) or hypnosis (Rainville et al., 2005), showing that pleasant emotions generally reduce pain while unpleasant emotions increase it. In a recent study, Rhudy and colleagues (Rhudy et al., 2005) demonstrated that the effect of emotional pictures was in part mediated by descending pain-modulatory pathways assessed by measuring the amplitude of a spinally mediated nociceptive reflex (nociceptive flexion reflex or RIII reflex; Sandrini et al., 2005). The reflex was largest in the context of unpleasant pictures, intermediate for neutral pictures and lowest for pleasant pictures, suggesting that positive emotions interfered with nociceptive processing at the level of the spinal cord. It is plausible that the same descending modulatory mechanisms are involved in the effects of music on pain.

In order to assess the influence of music on spinal nociception, we recorded RIII reflexes evoked by

moderately painful electric stimulations during the presentation of pleasant and unpleasant musical excerpts. In addition to the highly arousing pleasant and unpleasant musical excerpts used in our previous study (Roy et al., 2008), we also included pleasant excerpts with low arousal in order to test for arousal effects among pleasant excerpts. Indeed, there seems to be some disagreement about which type of pleasant music would be ideally suited to reduce pain. On one hand, healthcare providers intuitively use relaxing music for pain relief, based on the assumption that their anxiolytic properties are ideal to soothe pain (Good et al., 2005). At the opposite, Lang's motivational priming theory (Lang, 1995) proposes that arousal amplifies the effects of valence, and would therefore predict that pleasant-stimulating excerpts would have greater analgesic effects than pleasant-relaxing ones, as has been recently shown with high and low arousal pleasant pictures (Rhudy et al., 2008). The comparison of the effects of pleasant-stimulating and pleasant-relaxing music will therefore allow to test which of high- or low-arousal pleasurable music is more effective at reducing pain.

2. Materials and methods

2.1 Participants

A total of 30 healthy volunteers participated in the study (14 men, 16 women; mean age = 24.26 years, SD = 7.67). The Research Ethics Board of the 'Centre de recherche de l'Institut de gériatrie de Montréal' approved the study. All participants gave written informed consent and received a compensation of $20 for their participation.

2.2 Electrical stimulation

Transcutaneous electrical stimulation was delivered with a Grass-S48 stimulator (Astro-Med Inc., West Warwick, RI, USA) isolated with a custom-made constant-current stimulus-isolation unit. The stimulation consisted of a 30 ms train of 10 × 1 ms pulses, delivered on degreased skin over the retro-maleolar path of the right sural nerve by means of a pair of custom made 1 cm^2 surface electrodes. The intensity of the electrical stimulation was recorded (Biopac Systems Inc., Goleta, CA, USA) and the intensity of the stimulation was adjusted individually at 120% of the reflex threshold using the staircase method (Willer, 1977). This intensity minimizes ceiling and floor effects, and induces a stable and moderately painful pin-prick sensation.

2.3 Musical excerpts

Eight 1-min excerpts of pleasant-stimulating, pleasant-relaxing and unpleasant-stimulating[1] music were selected from a pool of 30 musical excerpts. Each of the 30 excerpts had been previously evaluated by 20 independent participants on the dimension of valence (on a scale ranging from 0 to 9 with 0 – 'pleasant' and 9 – 'unpleasant') and arousal (with 0 – 'relaxing' and 9 – 'stimulating') (Roy et al., 2008, 2009a). The pleasant-stimulating (valence: M = 2.40; arousal: M = 5.00) and pleasant-relaxing (valence: M = 2.68; arousal: M = 2.82) excerpts were matched on the valence dimension, whereas the pleasant-stimulating and unpleasant-stimulating excerpts (valence: M = 6.68; arousal: M = 5.18) were matched on the arousal dimension. All selections were normalized to equate loudness across musical excerpts by setting the peaks of the excerpts at 8% of the maximum volume allowed, using the normalisation option of the Cool Edit 2 sound editing software. A fourth condition consisting of 1-min long period of silence was included as a control condition.

2.4 Procedure

Before the experiment, all participants were provided with an overview of the experiment and informed consent was obtained. Then the participants were installed in a comfortable chair and the electrical stimulation was adjusted at 120% of each participant's RIII threshold, following the staircase method (Willer, 1977). The experiment was comprised of 26 experimental trials. The time course of a trial is depicted in Figure 1. Each trial consisted of the presentation of a

[1]Titles of the selected excerpts (title/album/artist). Pleasant-stimulating excerpts: (William Tell Overture/Rossini), (No. 5 g-moll. Allegro/Hungarian Dances/Brahms), (Russian Dance/Nutcracker/Tchaikovsky), (French Cancan/Cannissimo), (Love and Happiness/Now is the Time/Ernest Ranglin), (Water Trumpet concerto 3rd mvt/Haydn). Pleasant-relaxing: (Surfin'/Ernest Ranglin/Rebirth of the Cool #6), (Histoires sans paroles/Si on avait besoin d'une cinquième Saison/Harmonium), (The Blue Danube/Waltzes/Johannes Strauss), (Twenty Eight Parallel/1492/Vangelis), (Allegro ma non troppo/Symphony #6 "Pastorale"/Beethoven), (Novio/I Like to Score/Moby), Unpleasant-Stimulating: (Demon Sanctuary/Naked City/John Zorn), (Pendulum Music (Steve Reich)/Goodbye 20th Century (disc 1)/Sonic Youth), (Fascicles/The Thirteen Ghosts with Derek Bailey and Thurston Moore/Legend of the Blood Yeti (2 excerpts)), (Below the Walls of Jericho/The Threshold of Deafening Silence/Paul Dolden), (Caught in an Octagon of Unaccustomed Light/The Threshold of Deafening Silence/Paul Dolden).

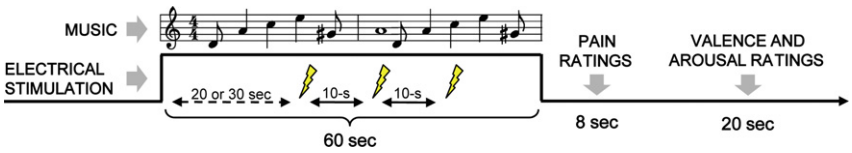

Figure 1. Time course of an experimental trial. Three electric stimulations are delivered at the 20th, 30th and 40th or 30th, 40th and 50th seconds within 60 s long musical excerpts or periods of silence. At the end of each musical excerpt, the participants rated the pain elicited by the electrical stimulations, and the emotions induced by the musical excerpt.

1-min long musical excerpt or silence period during which three electrical stimulations were delivered at either 20, 30 and 40 s, or 30, 40 and 50 s. The musical excerpts were presented using headphones (SONY MDRCD370, Toronto, Ontario, Canada) at a comfortable, individually adjusted, intensity level that remained constant across pleasant/unpleasant music conditions.

At the end of each musical excerpt, participants had 8 s to rate the pain elicited by the electrical stimulation on a visual analogue scale (VAS). They were asked to provide an overall rating of the pain induced by the three stimulations in the preceding block. They were also instructed that their pain ratings should reflect the perceived intensity (sensory dimension), as well as the discomfort (affective dimension) elicited by the electrical stimulations. The VAS was presented horizontally and included the verbal anchors 0 – 'no pain' and 100 – 'extremely painful' at the left and right extremities, respectively. After the participants had given their pain ratings, they were asked to rate the valence and arousal of the musical excerpts or silence condition using a computerized version of the Self-Assessment Manikin (Lang, 1980) (valence: 1 = unpleasant, 9 = pleasant; arousal: 1 = low arousal, 9 = high arousal).

Each experimental series started with two control trials in silence. These trials controlled for potential habituation effects, allowing for the RIII reflex to stabilize. Following these two trials, the remaining 24 trials were presented in a pseudo-random order consisting of six consecutive cycles, comprising each of the four experimental conditions (unpleasant arousing, pleasant arousing, pleasant relaxing and silence). These cycles were ordered so that no experimental condition was presented twice consecutively. Two orders of presentation were created (order 2 inverse of order 1) and their administration was counterbalanced across participants.

2.5 Physiological measurements and data processing

Electromyographic (EMG) activity of the biceps femoris was recorded with Ag-AgCl surface electrodes (Type EL-508, Biopac Systems Inc.) with an inter-electrode distance of 2 cm. EMG activity was amplified, band pass filtered (100–500 Hz), digitized and sampled at 1000 Hz (MP150, Biopac Systems Inc.). EMG data were analysed using Acknowledge 3.8 (Biopac Systems Inc.). The raw EMG data were transformed using the root mean square and the resulting signal was integrated between 90 and 180 ms post-stimulus onset to quantify the RIII-reflex to single shocks. Five participants (three women, two men) were excluded from the analyses because shock intensities at 120% of the RIII threshold could not be attained within the limits of pain tolerance.

The skin conductance response (SCR) was recorded on the palmar surface of the left hand, at the thenar and hypothenar eminences (EL-507 electrodes, Biopac Systems Inc.) at a sampling rate of 1000 Hz. The peak value of the SCR was extracted from a time window of 1–6 s following the electrical stimulation and the baseline skin conductance level in the 10 ms preceding the shock was subtracted from that peak value. SCRs were visually inspected and responses for which the baseline period was contaminated by a preceding spontaneous SCR were excluded from the analyses. Four subjects were excluded from the analyses because SCRs habituated rapidly and were absent in the second half of the experiment.

2.6 Data analysis

To confirm that the music elicited the target emotion, mean ratings of valence and arousal were averaged for each experimental condition and compared using a 4 (experimental condition) repeated measures MANOVA. Follow-up comparisons were conducted with Bonferroni adjusted means tests to control for Type I error rate. Pain ratings, RIII reflex amplitudes and SCRs were first standardized for each participant by converting them into *z*-scores in order to reduce inter-subject variability and normalize the distribution of the data (as in Rhudy et al., 2005 and Roy et al., 2009b). The resulting scores were then averaged for each condition and compared through a 3 (reaction type) × 4 (experimental condition) repeated measures

Table 1 Mean (±SD) valence and arousal ratings.

	Experimental condition			
	Unpleasant	Pleasant-stimulating	Pleasant-relaxing	Silence
Valence	2.40[b,c,d] (±0.90)	6.80[a,d] (±1.20)	6.67[a,d] (±1.27)	4.40[a,b,c] (±1.51)
Arousal	6.05[c,d] (±1.89)	5.71[c,d] (±1.83)	3.44[a,b] (±1.20)	3.23[a,b] (±2.26)

[a]Different from unpleasant.
[b]Different from pleasant-stimulating.
[c]Different from pleasant-relaxing.
[d]Different from silence.

MANOVA. Initially, participant sex was also included as an independent variable in all the models, but these effects and the corresponding interactions were not significant (Fs < 1.92, ps > 0.177). Thus, for parsimony, they were dropped from the final model. Pairwise differences between conditions were then considered with the appropriate follow-up contrasts. Partial eta-squared (η^2) was used as the effect size for F-tests and Cohen's d was used for mean comparisons. Cohen (1977) provides guidelines for interpreting η^2 (small = 0.01, medium = 0.06, large = 0.14) and d (small = 0.2, medium = 0.5, large = 0.8).

3. Results

3.1 Manipulation checks

Mean valence and arousal (SAM) ratings in each experimental condition are reported in Table 1. The ratings confirmed that the different musical excerpts effectively induced the intended emotions. Analysis of valence ratings revealed a main effect of the experimental condition [$F(3, 27) = 70.70$, $p < 0.001$, $\eta^2 = 0.89$]. Pleasant-stimulating and pleasant-relaxing excerpts were judged as more pleasant than unpleasant-stimulating excerpts, or the silence condition (pleasant-stimulating vs. unpleasant-stimulating: $p < 0.001$, $d = 4.15$; pleasant-relaxing vs. unpleasant-stimulating: $p < 0.001$, $d = 3.89$; pleasant-stimulating vs. silence: $p < 0.001$, $d = 1.75$; pleasant-relaxing vs. silence: $p < 0.001$, $d = 1.63$) and unpleasant-stimulating excerpts were rated as more unpleasant than the silence condition (unpleasant vs. silence: $p < 0.001$, $d = 1.60$). Pleasant-stimulating and pleasant-relaxing excerpts were judged as equally pleasant (pleasant-stimulating vs. pleasant-relaxing: $p = 1.00$, $d = 0.01$). Analysis of arousal ratings also revealed a main effect of the experimental condition [$F(3, 27) = 21.23$, $p < 0.001$, $\eta^2 = 0.70$]. Both pleasant-stimulating and unpleasant-stimulating excerpts were judged as more arousing than pleasant-relaxing excerpts or the silence condition (pleasant-stimulating vs. pleasant-relaxing: $p < 0.001$, $d = 1.46$; unpleasant-stimulating vs. pleasant-relaxing: $p < 0.001$, $d = 1.64$; pleasant-stimulating vs. silence: $p = 0.006$, $d = 1.21$; unpleasant-stimulating vs. silence: $p < 0.001$, $d = 1.35$). Note that pleasant-stimulating and unpleasant-stimulating excerpts did not differ on arousal ($p = 1.00$, $d = 0.18$), nor did pleasant-relaxing excerpts and the silence condition ($p = 1.00$, $d = 0.11$). All significant differences remained significant after applying the Bonferroni correction for multiple comparisons.

3.2 Pain ratings and RIII reflex

Mean pain ratings, RIII reflex amplitudes and SCR amplitudes, converted into z-scores, are reported for each experimental condition in Figure 2 (raw data are presented in Table 2). There was a significant effect of emotions induced by music on the multivariate combination of the standardized reactions [$F(3, 20) = 5.76$, $p = 0.001$, $\eta^2 = 0.68$] that interacted with the type of nociceptive reaction [$F(6, 17) = 2.97$, $p = 0.036$, $\eta^2 = 0.51$]. The effect of the experimental conditions

Table 2 Mean (±SD) raw pain ratings, RIII reflexes and skin conductance responses (SCRs).

	Experimental condition			
	Unpleasant	Pleasant-stimulating	Pleasant-relaxing	Silence
Pain ratings	49.67 (±24.24)	43.04 (±22.67)	42.13 (±23.49)	43.80 (±22.98)
RIII reflex (mV × s)	0.31 (±0.23)	0.29 (±0.21)	0.28 (±0.20)	0.26 (±0.19)
SCR amplitude (μS)	0.27 (±0.23)	0.25 (±0.22)	0.25 (±0.21)	0.23 (±0.18)

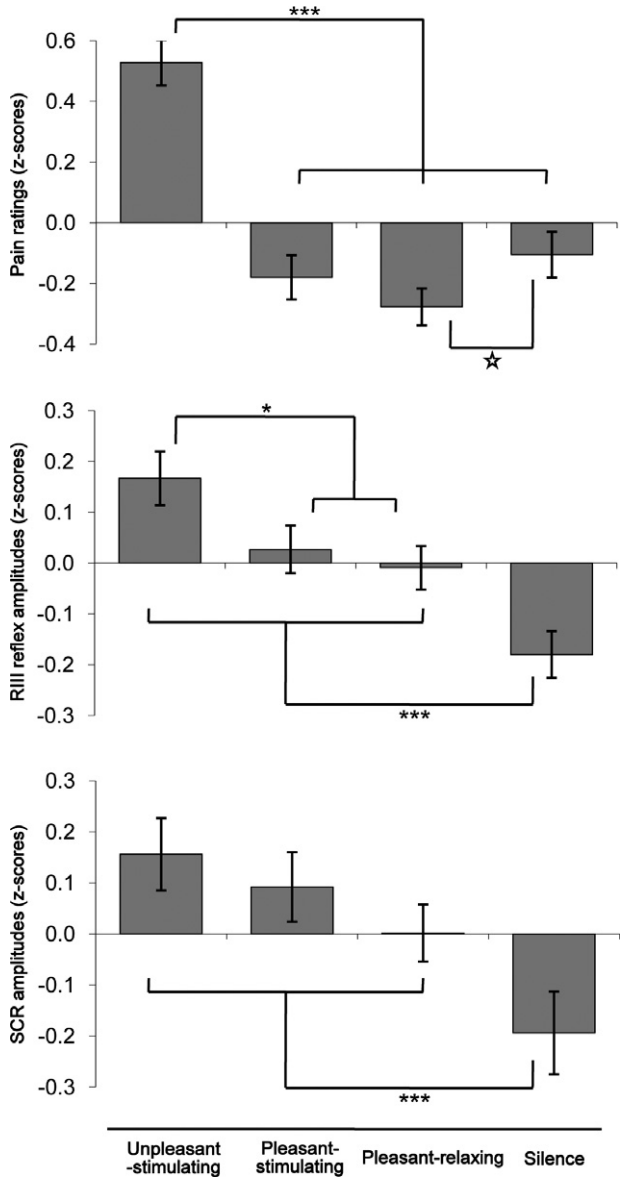

Figure 2. Mean pain ratings, RIII reflex amplitudes and skin conductance response (SCR) amplitudes (*z*-scores) for the four experimental conditions. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$, ☆$p = 0.09$, $p < 0.05$ one tail.

was significant for the 3 dependant variables [pain ratings: $F(3, 87) = 20.02$, $p < 0.001$, $\eta^2 = 0.40$; RIII reflex: $F(3, 72) = 6.82$, $p < 0.001$, $\eta^2 = 0.22$; SCR: $F(3, 75) = 3.77$, $p = 0.020$, $\eta^2 = 0.13$]. The main difference between the effects of music on the three types of nociceptive reactions was mainly due to the effects of the silence condition relative to the musical conditions. For pain ratings, there was no significant difference between the silence condition and pleasant-stimulating music ($p > 0.05$) and only a marginally significant decrease in pain ratings in the pleasant-relaxing music condition compared with silence ($p = 0.09$ two-tailed, $p < 0.05$ one-tailed, $d = 0.46$). However, RIII reflexes and skin conductance responses were lowest during the silence condition compared with the three musical conditions combined (RIII: $p < 0.001$, $d = 1.42$; SCR: $p < 0.05$, $d = 0.87$).

As expected, pain ratings were higher during unpleasant music than pleasant-stimulating ($p < 0.001$, $d = 1.75$) and pleasant-relaxing ($p < 0.001$, $d = 2.16$) music, but there were no significant differences between the pleasant-stimulating and relaxing music conditions ($p = 0.344$, $d = 0.35$). RIII reflex amplitudes were increased during the listening of unpleasant-stimulating excerpts compared with the pleasant-stimulating and pleasant-relaxing excerpts combined ($p = 0.038$, $d = 0.76$), but there were no significant differences between the pleasant-stimulating and pleasant-relaxing musical conditions ($p = 0.631$, $d = 0.20$). SCRs showed a pattern similar to the RIII reflex, but the difference between unpleasant-stimulating and the combination of pleasant-stimulating and pleasant-relaxing conditions was not statistically significant ($p = 0.197$, $d = 0.44$), nor was the difference between pleasant-stimulating and relaxing music ($p = 0.349$, $d = 0.38$).

4. Discussion

Pain perception was increased during the presentation of unpleasant musical excerpts compared with pleasant excerpts, replicating the valence effect observed on heat pain perception in a prior study (Roy et al., 2008). Moreover, this effect was paralleled by corresponding changes in RIII reflex amplitudes: RIII reflexes were higher during unpleasant than pleasant excerpts. This suggests that musically induced emotions influence pain in part through descending pain-modulatory pathways, as observed for emotional pictures (Rhudy et al., 2005). Finally, SCRs tended to show the same pattern of modulation as RIII reflexes, indicating that autonomic responses to painful electrical stimulations were also influenced by the valence of music, possibly as a result of the downstream modulation of nociception at the spinal level, impacting on the transmission of nociceptive signals to brainstem structures generating SCRs (Dawson et al., 2007).

One surprising result was the absence of reduction in pain ratings during the listening of pleasant-stimulating music compared with silence. This contrasts with the results of our previous psychophysical study showing a reduction in pain induced by thermal stimulations during the listening of pleasant-stimulating music compared with silence

(Roy et al., 2008), as well as with the effects of pleasant versus neutral pictures on pain induced by electric shocks (Rhudy et al., 2005, 2008). One reason for this discrepancy could be that the electric shocks were more surprising when subjects were paying attention to the music than during the silence condition, leading to an overall increase in pain ratings during all three musical conditions compared with silence. Indeed, the predictability of electric shocks has been shown to decrease pain ratings independently from the effects of emotions on pain (Rhudy et al., 2006). The interpretation of an overall increase in pain ratings during all music conditions relative to silence, combined with a classic effect of valence within musical conditions, fits well with our results showing a very large increase in pain ratings during unpleasant music compared with silence, but only marginally significant (pleasant-relaxing) or non-significant (pleasant-stimulating) decreases in pain ratings during pleasurable music conditions compared with silence. However, this increase in pain ratings during music versus silence could be absent when using tonic heat pain stimuli (Roy et al., 2008) because the onset of the thermal stimulation itself constitutes a warning cue about the upcoming pain, rendering the pain equally predictable across conditions. Although this interpretation remains speculative, a better understanding of the conditions under which pleasant emotions produce clinically meaningful decreases in pain compared with a no treatment condition would be primordial to the clinical application of emotion-induction procedures in pain management.

Another surprising result was the dissociation of pain ratings and RIII reflex amplitudes and SCRs when comparing pleasant musical conditions to silence. Although pain ratings were unaltered (pleasant-stimulating) or tended to decrease (pleasant-relaxing) during the presentation of pleasant musical excerpts compared with silence, RIII reflex amplitudes and SCRs did not parallel these effects and were surprisingly lower during silence compared with all other musical conditions. These findings are consistent with the results of a similar study conducted within our laboratory showing that RIII reflex amplitudes are higher and pain ratings are lower during the presentation of neutral pictures compared with a baseline condition with a fixation point (Roy et al., 2011). This dissociation between pain ratings (lower or unchanged) and RIII reflexes (increased) when attending to visual or auditory stimuli is also consistent with the results of several studies showing that the performance of a distractive cognitive task reduces pain but increases RIII reflex amplitudes (Petersen et al., 2001, McIntyre et al., 2006, Edwards et al., 2007). This dissociation between pain ratings and RIII reflex amplitude during distraction suggests that the increased spinal excitability observed during distraction may not specifically reflect spinal nociceptive processes, but may rather be due to an increased excitability of spinal motoneurones, as observed for other non-nociceptive reflexes (McIntyre et al., 2004). Thus, the lower RIII reflex amplitudes observed here during the silence condition should not be interpreted as reflecting reduced spinal nociception, but rather as reflecting the specific effects of distraction caused by music listening on spinal motor output.

Nevertheless, the comparison of the different musical conditions replicates the key finding of our previous study (Roy et al., 2008), showing that pleasant music decreases pain compared with unpleasant music matched for arousal. The present study extends these findings by showing that the valence of music also affects spinal nociceptive reflexes and SCRs. This suggests that, as for emotions induced by pleasant and unpleasant pictures (Rhudy et al., 2005, 2006), the effects of musical emotions on pain are partially mediated by descending modulatory mechanisms. The only difference observed with studies using pictures as the emotional inducer concerns the specific effects of pleasant and unpleasant stimuli relative to the control condition. However, this is not especially surprising since the control condition used in the present study, i.e., silence, is qualitatively different from the neutral pictures condition used in other studies (Rhudy et al., 2005, 2006) in that it does not control for competing sensory inputs. Obviously, a neutral condition that matches the emotional conditions on as many parameters as possible is a far better control condition than the mere absence of any stimulation. Indeed, we have demonstrated in a previous study that the mere presentation of neutral pictures can have serious effects on pain ratings and nociceptive reflexes (Roy et al., 2011). However, because of music's eminently emotional nature, finding such a neutral control condition with music is particularly challenging. The use of white noise could have provided a way to control for auditory stimulation, but pilot testing revealed that it tended to be judged as unpleasant, not neutral. Consequently, although the current results seem to only reveal a pro-nociceptive effect of unpleasant music, we advise caution when interpreting the differences between the musical conditions and the silence condition.

In contrast with the strong valence effects observed in the present study, the arousal of pleasant musical

excerpts did not produce any significant effect on pain. This lack of effect should be taken with caution considering the initially weak effects of pleasant music compared with the silence condition. Nonetheless, visual inspection of the mean differences in pain ratings, RIII reflexes and SCRs indicate a non-significant trend for pleasant-relaxing music to produce larger analgesic effects than pleasant-stimulating music. While pleasant-stimulating music did not significantly reduce pain as compared with silence, there was a marginally significant decrease in pain ratings in the pleasant-relaxing music condition as compared with silence. Although the effect is too weak to draw any strong conclusion about a possible analgesic superiority of relaxing pleasant music, these results seem to question the generalization of Lang's motivational priming model to musical material. Indeed, in Lang's motivational priming model, high arousal is thought to potentiate the effects of valence. For instance, in the appetitive domain, high arousal pictures (i.e., erotica) have stronger effects on defensive reflexes, such as the startle eye blink (Lang, 1980) or RIII reflexes (Rhudy et al., 2008), than low arousal pictures (i.e., food). However, the converse effect was seen here with pleasant-relaxing musical excerpts showing potentially stronger effects than pleasant-stimulating excerpts. This particularity of music could be linked to its fundamental role in calming young infants through their mother's singing, which appears to be universal (Trehub, 2003). If proven right, the capacity of music to effectively induce relaxing emotions could constitute one of the main advantages of music over other emotional inducers.

In summary, our results show that musically induced emotions can modulate pain processing at the level of the spinal cord, suggesting the involvement of descending pain-modulatory mechanisms. This finding adds onto prior findings that music can also modulate other defensive responses, such as the startle eyeblink reflex (Roy et al., 2009a) and stress-induced cortisol increases (Khalfa et al., 2003) and reinforces the idea that music is a powerful emotional inducer that can have a strong influence on pain.

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