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Pain-Related Nucleus Accumbens Function: Modulation by Reward and Sleep Disruption

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Summary:

This study contributes to our understanding of mechanisms supporting the association of sleep, reward, and pain by showing that sleep disruption attenuates nucleus accumbens activation during pain onset, and increases connectivity with the anterior midcingulate cortex when rewarding and noxious stimuli are presented at the same time.

Keywords

ventral striatum; nociception; fMRI; cingulate; sleep; positive affect

Introduction

Sleep and pain are strongly and reciprocally related, and both acute and chronic sleep disturbances increase experimental pain sensitivity and clinical pain reports [17; 42].

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However, treatments targeting sleep disturbance-induced hyperalgesia have yielded mixed findings [15]. Further, the neural mechanisms accounting for those associations are not completely understood, limiting our ability to translate basic findings into effective treatment. Accordingly, we designed the present study to evaluate the acute effects of experimental sleep disruption—a controlled laboratory sleep deprivation model paralleling the disrupted sleep chronic pain patients commonly report [18; 46]—on pain-related activation of the nucleus accumbens (NAc), using functional MRI (fMRI).

The NAc has dopaminergic inputs from mesolimbic structures as well as prefrontal areas including the medial prefrontal cortex (MPFC) and anterior cingulate (ACC) [38], which may be responsible for the NAc response to reward via pain relief [29; 34]. The NAc is functionally connected to ACC and MPFC at rest, and coactivated with basal ganglia, ACC, and insula [10]. Studies in humans and rodent models support a role of the NAc in pain processing and modulation, and considerable changes in NAc and its prefrontal inputs are observed following injury or chronic pain [7; 32]. The mesocorticolimbic system, which includes the NAc, is a critical modulator of pain [13; 47; 48; 54], with the NAc specifically implicated at the onset, and sometimes offset, of pain [2; 5; 9; 29; 35; 41]. NAc activation evoked by positive affect has also been reported to correlate with the extent of analgesia this produces, supporting the role of NAc in antinociception [53].

Total sleep deprivation increases NAc signal during anticipation and receipt of monetary rewards [33; 51; 52], or the perception of positively-valenced faces [21]. Yet, positive emotions and positive emotional pain inhibition, both of which enhance NAc activation [30; 55], are attenuated by sleep deprivation [18]. Two recent preclinical studies found that the pronociceptive effects of acute sleep deprivation were mitigated by adenosine antagonists in the NAc, potentially implicating dopamine receptor function in NAc neurons [1; 41]. Taken together, the extant literature implicates sleep as a modulator of NAc function, pain, and positive valence systems, including the rewarding effects of music [8; 39; 40]. However, the effects of sleep deprivation on NAc function in the context interacting pain and reward stimuli have not been reported.

We investigated the effects of experimental sleep disruption on pain-related NAc function in the context of a competing reward stimulus. We conducted a within-subject crossover experiment in which participants underwent a night of Uninterrupted Sleep and a night of experimental sleep disruption. After each condition, subjects completed an fMRI task where they were simultaneously exposed to noxious thermal stimuli and music of either rewarding or neutral valence. We hypothesized that: 1) NAc activation and connectivity are enhanced during pain onset and offset; 2) rewarding music attenuates activation and connectivity levels at pain onset and increases activation and connectivity at pain offset; and 3) sleep disruption reverses the effects of rewarding music on NAc activation and connectivity.

Methods

2.1 Participants

Twenty-one healthy, good sleepers (see Table 1 for criteria) were recruited for participation in this study (6 males, 15 females; 24.19 ± 4.2 y.o.). Subjects were concurrently enrolled in a

parent study (R01 DA032922, MTS) investigating the effects of two nights of experimental sleep disruption on hyperalgesia, inflammation, and morphine analgesia. An additional three subjects were initially enrolled in this sub-study but were removed for the following reasons: one individual had abnormal brain anatomy as determined by a radiologist, another had difficulties in operating the response box, and another had poor image quality due to interference from hair accessories that could not be removed. Subjects were recruited from the surrounding Baltimore, MD area through community fliers and electronic media platforms. This study was jointly conducted at Johns Hopkins Bayview Medical Campus and the University of Maryland Baltimore.

All protocols were approved by the Johns Hopkins University School of Medicine and University of Maryland Baltimore Institutional Review Boards, with all subjects completing informed consent prior to participation.

2.2 Study Design

The non-fMRI study procedures, including screening and sleep disruption procedures, have been previously described [18]. Figure 1 displays the sequence of tasks in the present study. Briefly, the parent study was a within-person experiment, with the order of sleep conditions randomized and stratified based on sex, body mass index (>25 vs. ≤25), age (18–32 vs. 33–48), and Chinese ethnicity (due to ethnic difference in morphine metabolism, related to parent study aims [57]. Morphine was not involved in the data collected for this sub-study). Eligibility procedures and inclusion/exclusion criteria are listed in Table 1. Participants were admitted to the clinical research unit (CRU) at Johns Hopkins Bayview Medical Center for each arm of the study. Following an adaptation night in which the subjects sleep was monitored via polysomnography (PSG), subjects received either one night of Uninterrupted Sleep or FA, followed by daytime assessments and an MRI scan the next day. There was a minimum 2-week washout period between sleep conditions. At the return visit, subjects did not undergo an additional PSG adaptation night prior to the sleep manipulation.

Uninterrupted Sleep: Subjects slept undisturbed during an 8-hour (480 minute) sleep opportunity.

Forced Awakenings: Briefly, the night was divided into eight 1-hour intervals. One of the hour-long intervals was randomly selected to be a 60-min awakening. The remaining seven hours were subdivided into three 20-min intervals, with one 20-min interval in each hour randomly chosen to be a period of awakening. During assigned awakenings, subjects were asked to sit up in bed and the room lights turned on to minimize the chance for microsleep. The maximum planned total sleep time opportunity during the Forced Awakenings protocol was 280 minutes. Subjects were not permitted to the leave the inpatient unit during sleep disruption periods, unless they elected to withdraw from the study.

2.3 Music Stimuli Acquisition

The selected rewarding and neutral music stimuli were used for both fMRI sessions.

2.3.1 Rewarding Music Stimuli—Following a PSG adaptation night, participants completed a music preference questionnaire where they were asked to create a list of up to 20 of their favorite songs that they associated with high positive emotionality and nostalgia. Nostalgia is a personally salient positive emotional state that is often evoked by music [3]. A playlist containing each of the songs was created on Spotify, and participants were presented with a 51-second clip of each song (the optimal song duration for the fMRI procedures). After listening to each song clip, subjects were asked to complete the Geneva Emotional Music Scales - 9 (GEMS-9) questionnaire [50; 56]. Participants rated the following emotions associated with the song clip on a scale of 1–5 (1=not at all, 5=very much): tension, power, joy, wonder, tenderness, transcendence, peacefulness, nostalgia, and sadness. We summed the ratings of power, joy, wonder, tenderness, and peacefulness and the 15 songs with the highest ratings were subsequently selected for inclusion in the fMRI procedures (see Supplemental Figure 1).

Selected songs were downloaded from iTunes and converted to .wav format via Faasoft Audio Converter. Songs were clipped to the first 51 sec using Audacity, and a two sec fade-in for the beginning of each song was overlaid. Lastly, songs were optimized for Sensimetrics S-14 MRI-safe headphones using EQ Filtering.

2.3.2 Neutral Music Stimuli—To establish the participant-specific neutral song pool, we exposed each participant to an assortment of songs from a large bank of songs that had appeared on the Billboard Top 100 charts in the 2000s, and that had been rated in a previous study as affectively neutral in a separate series of online music listening surveys [3; 26]. As with the rewarding music, we ensured that each neutral song selected for inclusion in the fMRI experiment were individually rated as “neutral” by each participant. Participants completed the GEMS-9 rating tension, power, joy, wonder, tenderness, transcendence, peacefulness, nostalgia, and sadness on a scale of 1–5 (1=not at all, 5=very much) at the conclusion of each song clip. This procedure was repeated until 15 songs were identified as having low positive emotion, low sadness, and low nostalgia for a given participant (e.g., ≤2). These songs were determined to be of neutral valence, and were subsequently used in the fMRI procedures for that participant. All neutral songs were popular hits following typical modern musical genres similar to the rewarding songs. Playlists for each participant were customized so that neutral stimuli were not personally significant or emotionally evocative. This was done to increase the likelihood that valence-based differences reflect the superior hedonic and personally salient value of the rewarding music.

2.4 MRI Procedure

2.4.1 Pre-scan Activities—Prior to the scan session, subjects completed a series of questionnaires and computer tasks assessing speeded responses to cognitive and affective stimuli. These measures were collected at the Johns Hopkins Clinical Research Unit, typically beginning around 10:00am. Lunch was typically served around 12:00pm. Subsequently, participants were transported to the imaging center at University of Maryland-Baltimore. Upon arrival, participants underwent preliminary quantitative sensory testing and response box practice.

Determination of Painful Heat Stimulus: Prior to the start of the MRI session, subjects were asked to rate a series of thermal heat stimuli (42–48°C) applied to their left medial forearm using an fMRI-compatible quantitative sensory testing thermode (30 × 30mm Medoc Pathway model ATS, Medoc Advanced Medical Systems, Ramat Yishai, Israel). The temperature that would be used for the functional portion of the MRI scan was rated as a 6–9 on a 0 (no pain) to 10 (worst pain imaginable) pain intensity scale/ visual analog scale. For determination of temperature, we used a ramp and hold protocol wherein temperatures were delivered for 8 seconds before returning to a baseline temperature of 35°C. The first temperature administered was 42°C. Temperatures were increased by increments of 2°C until subjects rated pain at least 6/10 and no more than 9/10.

Response Box Practice: Before entering the scanner, subjects completed a practice task to become familiar with how to properly record ratings to pain and music stimuli once in the scanner using a response box. Participants were seated at a computer and using the keypad and their right hand, were asked to match a numerical word (one – ten) that appeared on the screen with its numerical value. The starting numerical value was 5. From there, subjects could press the 1 or 3 button on the keypad to decrease or increase the displayed numerical value, respectively. When the numerical value matched the word, subjects locked in their responses by pressing the 2 button. Subjects had three seconds to match the number to the word. When the subject felt comfortable with the task, they were prepped for the scanner.

2.4.2 MRI session

Parameters: Each MRI session included one anatomical scan and three functional runs. All scans were acquired at the University of Maryland, Baltimore Medical Imaging Facility using a Siemens 3T Tim Trio scanner equipped with a 32-channel head coil. Participants underwent a high-resolution T1-weighted MPRAGE anatomical scan (240 slices, TR 2300ms, TE 2.98ms, flip angle 9°, FOV 256mm, matrix 256 × 256mm, resolution 1.0 × 1.0 mm, slice thickness 1mm, no gap) and three functional runs using interleaved T2*-weighted, echo planar imaging (EPI) sequences (spin-echo, 922 volumes/run, 66 slices, TR: 907ms, TE: 30ms, flip angle 52°, FOV 224mm, matrix size 110 × 102mm, resolution 2.0 × 2.0mm, slice thickness 2.0mm, multiband factor 6). Each functional run consisted of 922 volumes, lasting 13min 56s.

Delivery of both the audio and visual stimuli for the anatomical and functional scans was coded and run using Presentation (Neurobehavioral Systems, Berkeley, CA) via a desktop computer. Visual stimuli were back-projected onto a translucent screen positioned behind the scanner bore and viewed from an angled mirror mounted on the head coil positioned at subject's eye-level. MRI-compatible corrective lenses were available upon request to assist with viewing the screen.

Anatomical: During the anatomical scan, subjects performed a modified version of the Attentional Network Test [14], which involved indicating the directionality of an arrow that appeared on screen using the response box that was positioned in their right hand. This task was done to maintain alertness, reduce movement, and minimize the risk for microsleep while in the scanner.

Functional: An illustration of the scan sequence can be viewed in Figure 2. There were 30 trials total (10 trials/run, 3 runs). At the start of each trial, a music stimulus (rewarding or neutral) would be selected at random (without replacement) from the designated folder. Following the start of the music stimuli presentation (tailored for each subject), warm and painful heat stimuli were administered for a duration of 7.4–10.4 seconds and 10.4–13.4 seconds, respectively, with onsets (ramp to designated temperature from baseline) for both thermal stimuli being 3 seconds, while offsets (ramp down to baseline) were 1.6 seconds for both thermal stimuli. The offset was faster than the onset because we wanted to capture an unambiguous period of pain relief. Pain offset occurred prior to music offset. Warm and painful heat stimuli were separated by 7–10 seconds of baseline temperature (35°C). While the warm stimulus always preceded the heat stimuli, the onsets and durations of each stimulus were pseudorandomized to minimize expectation effects. Warm stimuli were included as a control for non-pain-specific effects, as described below. At the conclusion of each trial, subjects used an MRI-compatible response box to rate the following associated with the thermal and music stimuli: pain intensity, pain unpleasantness, music liking, music joy, and nostalgia on a scale of 0 (no pain/ no liking) to 10 (worst pain imaginable/ like very much).

2.4.3 fMRI preprocessing—

Preprocessing was performed in SPM12 v6906 (http://www.fil.ion.ucl.ac.uk/spm/) and included realignment (motion correction), coregistration of the T1 anatomical to the mean functional image, segmentation of the anatomical to six standard tissue probability maps in SPM12, normalization of the functionals using forward deformation fields from anatomical segmentation, output 2×2×2 mm voxels (same as acquisition), and smoothing of functionals at 6mm full-width at half maximum (FWHM). Quality control included visual inspection at all stages of preprocessing.

2.4.4 fMRI First Level Analysis—

For each subject, a general linear model with timings for regressors of interest as well as motion parameters of no interest were included. Canonical hemodynamic response function was applied to regressors of interest, model derivatives were not included because of the block-within-block design of the study, a high-pass filter of 0.0078 Hz was applied, and correction for serial correlations was performed using the FAST algorithm [49]. The following conditions were modeled for both positive and neutral music valence: music (note: music conditions represent the first 4 to 11 sec of the song when no other stimuli is present), warm onset (3 sec), tonic warm (7.4–10.4 sec), warm offset (1.6 sec), pain onset (3 sec), tonic pain (10.4–13.4 sec), pain offset (1.6 sec), and ratings (during which subjects recorded their responses to the thermal and music stimuli). Model parameters were estimated using the ReML algorithm [19].

2.4.5 Second Level Analyses

2.4.5.1 Whole Brain Analyses: Group-level statistics were performed using the first level contrast estimates entered per subject for the Uninterrupted Sleep sessions to identify neural effects of rewarding music under “normal” conditions. We performed whole-brain analysis on the contrasts that we hypothesized would be associated with activation of the NAc. These included one-sample t-tests for pain onset, tonic pain, and offset during neutral music. To demonstrate that NAc is transiently activated at pain onset, we created peristimulus plots for

the NAc (using the activated cluster) and other regions of interest activated at pain onset (using 10mm spheres centered on the local maxima for each peak in bilateral anterior and posterior insula and midcingulate cortex) by extracting the percent signal at each TR using MarsBar (http://marsbar.sourceforge.net/).

We also performed these analyses using warm stimuli as the baseline (i.e. pain onset vs warm onset, tonic pain vs tonic warm, pain offset vs warm offset). Additional whole brain paired t-tests compared Forced Awakenings to Uninterrupted Sleep on NAc activation. Analyses used a cluster-forming threshold of $p<0.001$ and were corrected for multiple comparisons at the cluster level ($p<0.05$, FWE).

2.4.5.2 ROI Analyses: Because the hypotheses focused on NAc activity, we performed ROI analyses of this region. ROIs were created for the left and right NAc based on the AICHA atlas [27]. We also divided the cluster bilaterally. We extracted the betas for all conditions of interest and performed mixed effects modeling using the within-subjects factors sleep (US, FA) and valence (neutral, rewarding), for pain onset, tonic pain, and pain offset. To demonstrate the effects of NAc across the whole experimental paradigm, we also extracted betas for the warm conditions (onset, tonic, offset).

2.4.5.3 Psychophysiological Interaction (PPI): In order to determine the connectivity of the NAc during pain onset, we used a PPI analysis. Psychophysiologic regressors were extracted using the generalized PPI toolbox v13.1 [31]. The seed region used was the bilateral NAc cluster from the Uninterrupted Sleep pain onset, neutral music one-sample t-test, described above. NAc psychophysiologic regressors were created in the Uninterrupted Sleep and Forced Awakenings states separately for pain onset during rewarding and neutral music.

First level analyses were performed in SPM12 using the PPI regressors of interest along with task regressors for each of the relevant conditions, an activity regressor for the seed region, and six motion regressors. Other first level parameters were identical to those described above. Second level analyses began with a one-sample t-test for pain onset (US, neutral music) to examine the connectivity of NAc during pain onset. Modulation of those brain regions was examined across the whole brain. These included three analyses: 1) paired t-tests for pain onset during rewarding music vs. pain onset during neutral music (to examine the main effect of rewarding music on NAc connectivity during pain onset); 2) paired t-tests for pain onset during neutral music under Uninterrupted Sleep and Forced Awakenings (to examine the main effect of sleep on NAc connectivity during pain onset); and 3) a flexible factorial model of pain onset during rewarding vs. neutral music by Forced Awakenings vs Uninterrupted Sleep (to investigate the interaction between sleep and valence on NAc connectivity during pain onset). All results are reported at a cluster-forming threshold of $p < 0.001$, with FWE correction for multiple comparisons at the cluster level.

Results

3.1 Participant Characteristics

Participant demographics are listed in Table 2. Overall, the sample was composed of healthy, educated, and relatively young individuals. During the period in which this sub-study occurred, the parent study had greater recruitment and enrollment of females (N = 15; 71.4%) than males (N = 6; 28.5%). Participants were ethnically and racially diverse, with 52.4% reporting as non-Caucasian.

3.2 Sleep Manipulation Check

As a manipulation check, we compared sleepiness ratings on the Stanford Sleepiness Scale [25], a validated measure of subjective sleepiness commonly used in sleep deprivation studies [24], between sleep conditions. Results confirmed that participants were significantly sleepier at the time of the fMRI procedures (1:30pm) following Forced Awakenings (M=2.84; SD=1.43) relative to Uninterrupted Sleep (M=1.95; SD=0.78), [t = 3.26, $p = .02$].

3.3 Behavioral Ratings

Descriptive statistics for self-reported ratings of positive emotion, nostalgia, pain intensity, and pain unpleasantness are summarized in Table 3. Positive emotion [B=−3.80 (SE = .18), t = −21.48, $p < .001$] and nostalgia [B = −4.52 (SE = .21), t = −21.43, $p < .001$] were significantly lower under neutral relative to rewarding music, providing supportive evidence that the stimuli elicited the expected subjective effects.

Pain ratings varied within-subject as a function of stimulus valence; both pain intensity [B = .69 (SE = .10), t = 6.83, $p< .001$] and pain unpleasantness [B = 1.05 (SE = .12), t = 9.03, $p< .001$] were significantly higher during neutral relative to rewarding music. These findings suggest that rewarding music was acutely analgesic. Across valences, pain intensity (B = .29 (SE = .09), t = 3.25, $p = .001$), but not pain unpleasantness ($p = .78$), was significantly higher following Uninterrupted Sleep compared to FA. There was no Sleep Condition X Valence interaction on pain intensity ($p = .59$) or pain unpleasantness ($p = .32$) ratings.

3.4 NAc fMRI Activation Analyses

3.4.1 Onset of Pain Activates the NAc—

Whole brain analyses revealed significant activation in the bilateral NAc at the onset of painful thermal stimuli during neutral music (Figure 3A). Whole brain comparisons of pain onset versus warm onset during neutral music also revealed NAc activation, which did not meet our pFWE corrected threshold. However, with small volume correction at an 8mm sphere – covering most of the NAc – the cluster was significant (pFWE = 0.008; Supplemental Figure 2). The peristimulus plots demonstrate that NAc was activated at pain onset, in contrast to insula and cingulate ROIs, which has more sustained responses (Figure 3B).

Significant NAc activation was not observed during tonic pain or the offset of painful thermal stimuli during neutral music. Table 4 displays the complete list of activations and deactivations at each pain period.

Additional whole brain analyses are presented as Supplemental Figures 2 and 3.

3.4.2 Music Valence Does Not Significantly Modulate NAc Activation During Pain—ROI mixed effects models did not reveal a significant main effect of valence on NAc activation at pain onset, tonic pain, or pain offset (see Table 5), indicating that rewarding versus neutral music did not have significantly differential effects on NAc activation during pain.

3.4.3. Sleep Disruption Modulates NAc Activation, Irrespective of Valence, During Pain Onset and Tonic Pain—ROI mixed effects models showed significant main effects of sleep condition on NAc activation with significant effects for both the left NAc (p = .01) and right NAc function (p = .04) at pain onset (Table 5 and Supplemental Tables 1 and 2). Both effects indicated reduced NAc activation at pain onset following Forced Awakenings relative to Uninterrupted Sleep (Figure 3 C, D).

There was also a main effect of sleep condition on the left NAc function during tonic pain (p = .02; Table 5 and Supplemental Table 3), indicative of increased left NAc activation following Forced Awakenings relative to US. Figure 3 C, D shows the effect of each condition on activity in the left NAc ROI across conditions (pain onset, tonic pain, pain offset).

Sleep condition and valence did not significantly interact to predict either left or right NAc activation during pain onset, tonic pain, or pain offset periods (p's ≥ .74; see Table 5), suggesting that the effect of Forced Awakenings on pain-related NAc activation was not reliant upon music valence. Plots of all conditions – including warm stimulus conditions – are presented in Supplemental Figure 4.

3.4 fMRI Psychophysiological Interaction Analysis of the NAc

To further investigate the role of NAc in the intersection of pain, sleep, and reward, we used PPI analysis with the NAc ROI derived from the significant cluster in the pain onset (neutral music, US) analysis. We first examined connectivity of the NAc at pain onset during neutral music and following US. NAc showed strong connectivity to the bilateral thalamus, S2, basal ganglia, posterior midcingulate cortex (pMCC), anterior midcingulate cortex (aMCC) (Figure 4A, Table 6). There was a significant main effect (following US) of Valence in a cluster in the medial orbitofrontal cortex (OFC) (MNI coordinates 6, 30, −14, T=5.18, pFWEcorr = .022) at pain onset during rewarding relative to neutral music. There was not a significant main effect of Sleep Condition NAc connectivity. However, there was a significant Sleep Condition X Valence interaction (pFWEcorr = 0.010) on the same aMCC cluster (Figure 4B) identified in the PPI of pain onset, reflecting a reward-related reduction in connectivity at pain onset during Uninterrupted Sleep that was not observed following Forced Awakenings.

Discussion

The primary findings of the present study are: 1) the NAc is activated by the onset of painful thermal stimuli, but not during tonic pain or pain offset; 2) rewarding music activates NAc

and alters NAc connectivity with key nodes of the corticostriatal circuits during pain onset; and 3) sleep disruption is associated with both attenuated NAc activation and increased reward-related connectivity between the NAc and the aMCC at pain onset.

NAc is Activated at Pain Onset

Our results revealed strong activation of the NAc over the onset period of an ascending noxious thermal stimulus when participants were well-rested, consistent with prior research showing that the NAc is involved in salience detection for aversive stimuli [11; 48]. It adds to the mixed body of work that has investigated NAc function specifically during pain, supporting prior work showing increased NAc activation at thermal pain onset [2; 5] and increased activation in posterior striatal areas during aversive learning [43; 44]. Two other studies have reported decreased NAc activation at thermal pain onset, but it is not clear the extent to which those findings can be compared to the present results due to diverging methods [4; 6]. Other work has shown decreased NAc signal during non-painful punishments [12]. A notable difference in our study is that noxious thermal stimuli were paired with music of either neutral or positive (i.e., rewarding) valence. We used this design because we were interested in understanding the extent to which pain-related NAc activation is modulated by reward, and if those processes are, in turn, altered by sleep disruption. We employed a novel, personalized music delivery model in which participants chose as their rewarding stimuli personally relevant song clips that specifically elicited positive emotions. These songs were contrasted with neutral songs that were similar in quality, bore no personal significance, and were explicitly rated as devoid of positive or negative emotional value.

NAc Activation at Pain Onset is Modulated by Reward

The presentation of noxious thermal stimuli concomitant with the continuous music yielded a novel context to observe pain-related NAc function. Given the increased positive emotionality engendered by the rewarding music, we assumed that the painful stimulus was more salient when presented during neutral relative to rewarding music [36; 37]. To that end, participants registered significantly higher pain intensity and unpleasantness ratings during neutral relative to rewarding music, even though the magnitude of the painful stimulus did not vary throughout the task. We expected that rewarding music would attenuate NAc signal during pain onset, but only observed a statistical trend in that direction for the right but not left NAc. It is possible that the effect of rewarding music on pain-related NAc function would have been stronger if contrasted to negative instead of neutral music; indeed, affective pain modulation studies have consistently shown that the valence effects on self-reported pain intensity are stronger for the positive/negative relative to the positive/neutral contrast [16].

Nonetheless, we did observe increased NAc connectivity to the orbitofrontal cortex (OFC) and decreased NAc connectivity to the aMCC at pain onset during rewarding relative to neutral music, only in the normal sleep condition. Preclinical work has demonstrated that dopaminergic projections to and from the NAc functionally define an integrated set of corticostriatal circuits, of which the OFC and aMCC are key nodes [22; 23] and that afferent projections to the NAc are associated with antinociception, whereas efferent projections from the NAc are associated with pronociception [20]. Consistent evidence has implicated

the OFC in the valuation of rewarding stimuli [28]. The aMCC is robustly linked to cognitive control of aversive experiences, including pain[45]. That rewarding music was, at once, associated with increased NAc-OFC connectivity and decreased NAc-aMCC connectivity during pain onset suggests that it diminished the strength of the efferent projections from the NAc supporting cognitive control of pain in favor of efferent activity supporting reward valuation.

Notably, we did not observe NAc activation differences during tonic pain or pain offset, irrespective of valence. Although we hypothesized there would be increased NAc activation at pain offset based on prior literature that had indicated pain offset [2; 4; 6] and cues for pain relief [29] were associated with NAc activation, those studies may not directly comparable due to substantial design variability (e.g., inclusion of rewarding and neutral music stimuli overlaid on the pain periods).

Sleep Disruption Decreases NAc Activation at Pain Onset and Increases NAc Activation During Tonic Pain

We observed bilateral reductions in NAc activation during pain onset as a function of sleep disruption. Despite findings from the broad literature linking sleep disturbances to increases in pain, we found that sleep disruption attenuated NAc activation. In our experimental design, noxious stimuli were delivered concomitant with other affective stimuli competing for cognitive resources. A speculative possibility that should be explored in future studies is that sleep disruption reduces the phasic dopaminergic response in the NAc, resulting in decreased activation during the detection of aversive stimuli when such stimuli are in competition with other cognitively and affectively salient stimuli.

In contrast to its role in diminishing NAc activity during pain onset, sleep disruption was associated with greater NAc BOLD signal during tonic pain compared to normal sleep. This raises the possibility that sleep may dynamically modulate pain-related NAc activation at different stages of a pain stimulus. As the pain onset gave way to a period of tonic pain, NAc remained active in the sleep-deprived state despite returning to baseline under normal sleep. Thus, under Uninterrupted Sleep, the NAc responded to the initial delivery of noxious stimuli and subsequently deactivated during tonic pain, whereas this dynamic responsiveness of the NAc was blunted following sleep disruption. These findings could reflect a delayed threat evaluation in the sleep deprived state, whereby the absence of overt threat appraisal gives way to a counter-regulatory mechanism (e.g., analgesia) which may be represented by a delayed activation when the stimulus is fully perceived. Of course, this interpretation requires further investigation, perhaps in a pre-clinical model with greater sensitivity to evaluate these temporal contingencies. An alternative interpretation is that sleep disruption blunts top-down control over pain. Given the role of NAc in pain modulation [7], the increased NAc activation may reflect a lack of top-down cortical inhibitory input to the NAc. The PPI analysis addresses this possibility.

Sleep Disruption Alters Reward-Related NAc Connectivity at Pain Onset

NAc-aMCC connectivity at pain onset was decreased by rewarding music following Uninterrupted Sleep, but this modulation was not seen following Forced Awakenings. This

can also be interpreted as a relatively increased reward-related connectivity with the aMCC, reflecting a recruitment of this region to recover cognitive control of pain following sleep disruption. This alteration in reward-related modulation of NAc during pain could also be related to the reduced phasic dopaminergic response in the NAc, as suggested above.

Limitations

There were three main limitations to the study. First, we did not include a functional block in which painful thermal stimuli were delivered without accompanying music, prohibiting a direct comparison of reward-inhibited pain to pain alone. Second, there was an imbalance between males and females, prohibiting our ability to probe sex differences. As stated earlier, this was due to an unintentional bias in recruiting during the parent study. Third, also associated with the parent study design, we could not evaluate the effects of recovery sleep on the measures evaluated in this study. These limitations were balanced by several notable strengths, including the within-subject, crossover sleep disruption design, the use of a neutral music control and a tailored thermal stimulus protocol.

Summary and Conclusions

The present results reveal that the NAc is activated at pain onset under neutral music conditions, followed by a relatively quick deactivation during tonic painful stimuli, and that one night of sleep disruption reverses these patterns. Furthermore, at pain onset, NAc connectivity with key cortical regions underlying reward valuation (OFC) and cognitive control (aMCC) is modulated by rewarding music under normal sleep. Following sleep disruption, the NAc-aMCC circuit is relatively enhanced when rewarding music overlays the onset of pain. This is the first human study, to our knowledge, to investigate changes in neural processing of noxious stimuli, and the combination of noxious and rewarding stimuli, following experimental sleep disruption.

These findings contribute to our understanding of mechanisms supporting the association of sleep, reward, and pain by showing that sleep disruption attenuates NAc function during the period of salience evaluation, and increases reward-related connectivity with the aMCC, a region commonly associated with the volitional attempt to use cognitive resources to regulate pain [45]. The findings highlight the complexity of these relationships and suggest that additional experimentally controlled studies are needed to better understand the macro-level data supporting the commonly held notion that sleep loss is hyperalgesic [17]. Future studies should examine changes in neural processing of noxious stimuli presented alone versus those presented in combination with affective stimuli. Altogether, these findings suggest that sleep disruption has a profound effect on both the detection and processing of aversive stimuli that may have important implications for chronic pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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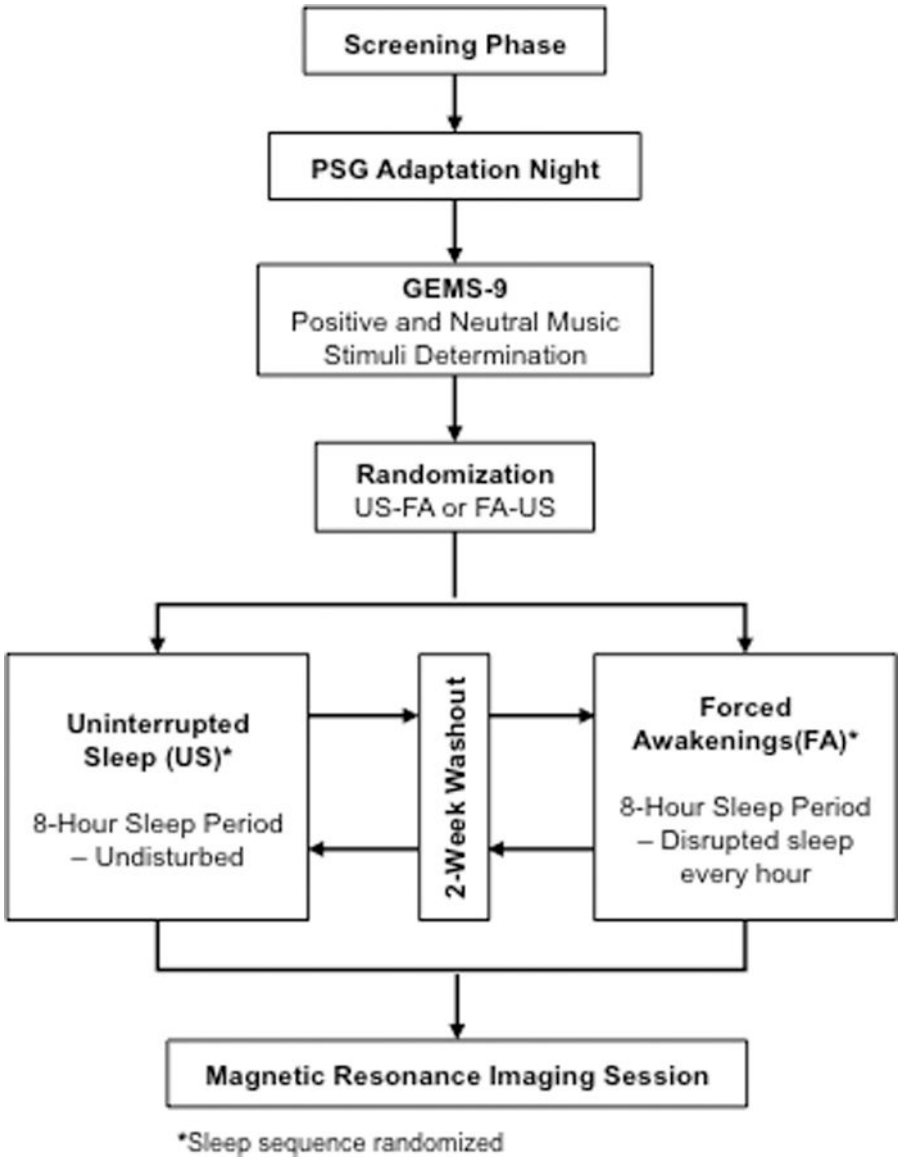

Figure 1. Study design flow.

Following initial screening, subjects underwent an adaptation night in which their sleep was monitored via PSG. The next day, subjects completed the GEMS-9 to determine the positive and neutral music stimuli that would be used during the functional imaging section of their MRI scan. Following a night of either Uninterrupted Sleep or FA, subjects underwent an MRI scan. After a two week washout period, subjects were brought back in to receive the opposing sleep condition and undergo a second MRI.

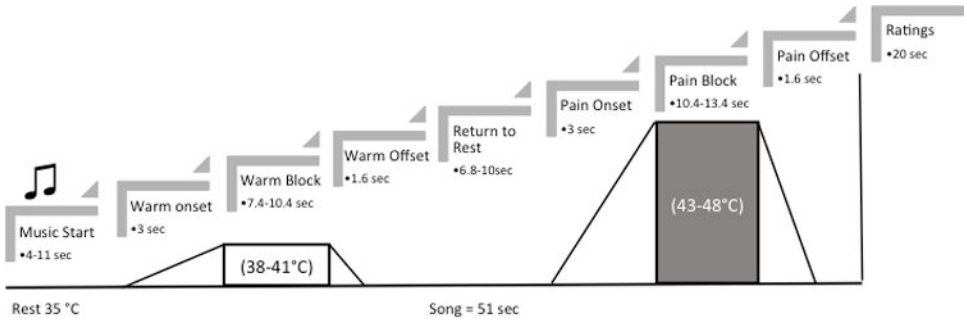

Figure 2. Functional run design.

Each MRI session was comprised of three functional runs, with 10 songs per run (5 positive, 5 neutral). Songs were clipped to 51 sec and played in random order. Following a brief period of only music stimuli playing, the thermal stimuli would be presented. Warm stimuli preceded painful heat, respectively, while their durations were pseudorandomized. At the conclusion of each song, subjects had 20 seconds to rate the following on a scale of 0 to 10: pain intensity, pain unpleasantness, music liking, music joy, and nostalgia.

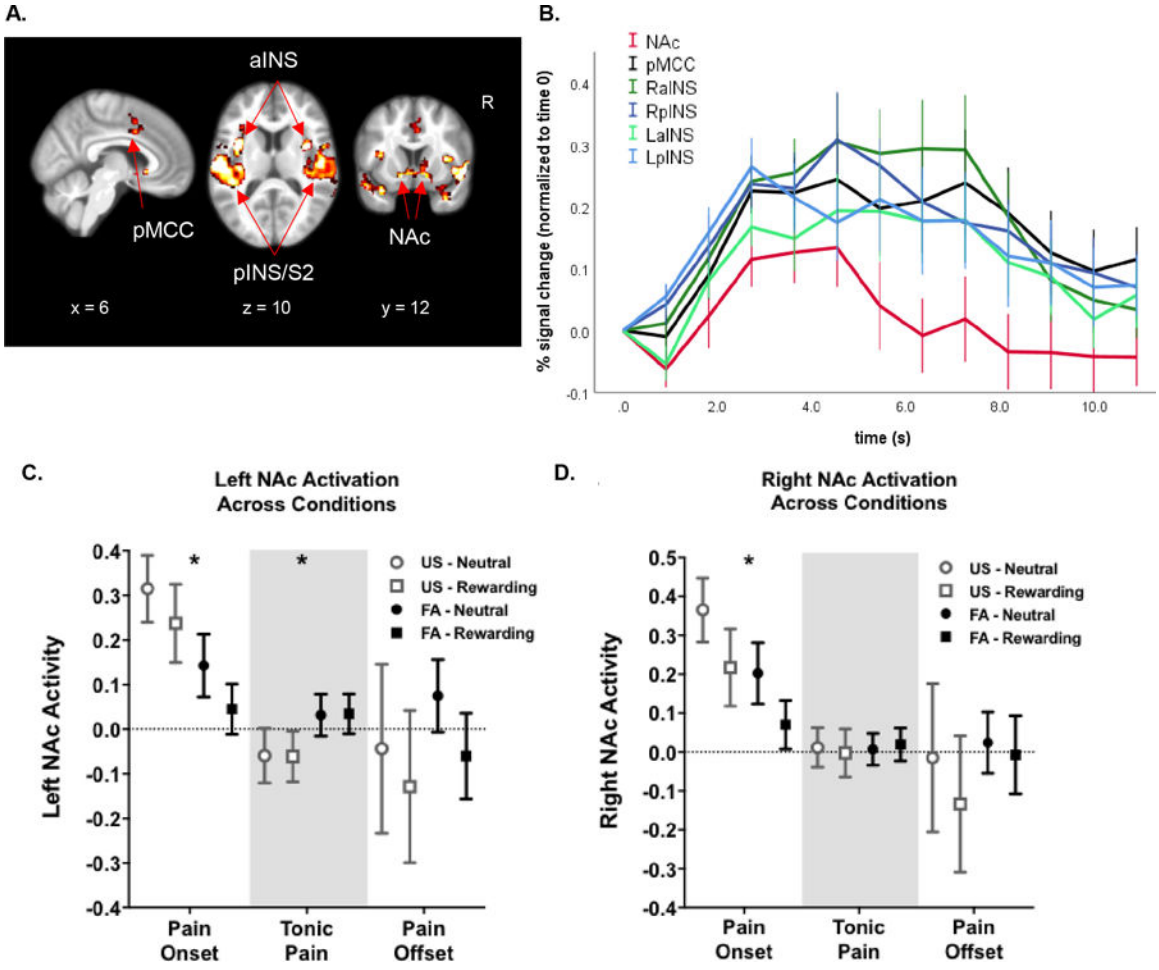

Figure 3. NAc activates at pain onset.

A) Activation associated with pain onset during neutral-valence music following Uninterrupted Sleep. Cluster-forming threshold p<.001, FWE-corrected clusters shown. Overlay images thresholded from t = 3.5 to 5.5. R, right side of brain. B) Peristimulus plots for activated regions, showing NAc has a clear transient activation. C, D) NAc activation was significantly greater for pain onset following Uninterrupted Sleep (US) compared to Forced Awakenings (FA) on both the left and right NAc. The left NAc showed greater NAc activation following forced Awakenings compared to Uninterrupted Sleep for tonic pain (*p<.05). A trend was observed for greater NAc activity at pain onset for neutral compared to rewarding music. The NAc ROIs are from the AICHA atlas. Graphs represent mean ± SEM.

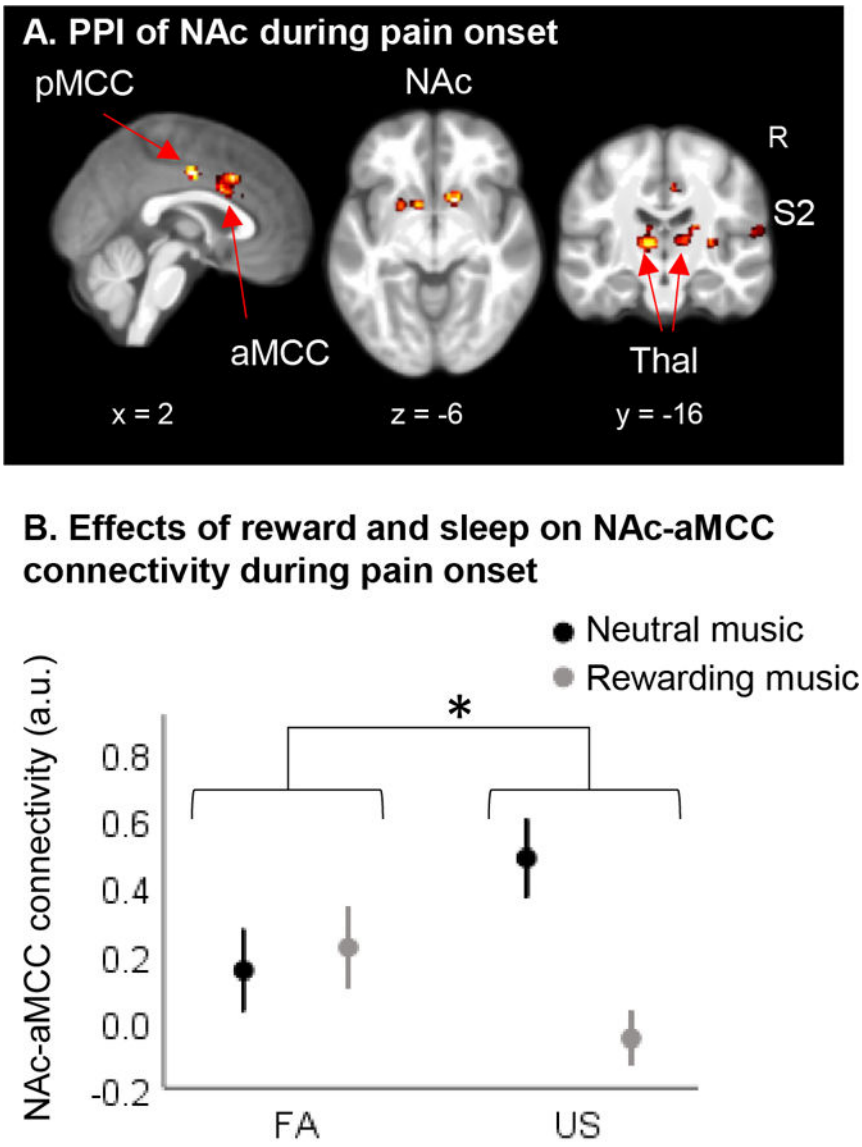

Figure 4. PPI of NAc during pain onset.

A. Connectivity of NAc at pain onset during neutrally-valenced music following normal sleep. Cluster-forming threshold p<.001, FWE-corrected clusters shown. Overlay images thresholded from t = 3.5 to 5.5. R, right side of brain. **B.** Effects of reward and sleep on NAc-aMCC connectivity. Rewarding music was associated with a significant reduction in NAc-aMCC connectivity, and while no main effect for sleep was observed, the sleep-by-valence interaction was significant (*p<.001). Graphs represent mean ± SEM. US, Uninterrupted Sleep; FA, Forced Awakenings.

Table 1.

General Inclusion and Exclusion Criteria

Inclusion Criteria
• Healthy, 18–48 years old, meeting the Research Diagnostic Criteria for Normal Sleepers
• Non-smoker/nicotine user
• Low caffeine users (≤ 2 cups of coffee or equivalent per day)
• Stable sleep phase within 21:00 and 10:00
• Pittsburgh Sleep Quality Index Total Score < 5
• Total sleep time between 6.5 and 8.5 hours/night; sleep efficiency ≥85%; Epworth Sleepiness Scale <10 (confirmed with averages of 2 weeks of sleep diary and actigraphy monitoring)
Exclusion Criteria
• BMI ≥35
• History of chronic pain (lifetime history of pain persisting for ≥6 months)
• Acute pain (measured via McGill Pain Questionnaire and 2 weeks of baseline sleep diaries)
• Significant medical/ psychiatric morbidity within 6 months or lifetime history of: bipolar disorder, psychotic disorder, recurrent major depression, posttraumatic stress disorder, or seizures
• Significant symptoms of psychological distress (T-scores >64 on the Brief Symptom Inventory global scales)
• Respiratory, hepatic, renal or cardiac conditions that would contraindicate opioid administration
• Lifetime history of substance abuse or dependence, including: alcohol; opioid use >36 doses or >7 days consecutive use
• Prior adverse reactions to general anesthetics/opioids or capsaicin
• Clinically significant abnormal complete blood count or comprehensive metabolic profile
• Positive toxicology screen for recreational drugs (THC), stimulants, opioids or benzodiazepines
• Pregnant or lactating women
• Polysomnography-confirmed apnea-hypopnea index < 10
• Significant lifetime history of serious head injury that is judged to influence pain processing or sleep systems

Table 2.

Demographics

Total Participants	**21**
Age (Mean ± SD)	24.19 ± 4.2
Sex, n (%)	
Female	15 (71.4%)
Male	6 (28.6%)
Race, n (%)	
Caucasian	10 (47.6%)
African American	6 (28.6%)
Asian	2 (9.5%)
More than one race	2 (9.5%)
Other/Decline to State	1 (4.8%)
Ethnicity	
Hispanic/ Latino	6 (28.6%)
Education, n (%)	
Some College / Current Student	10 (47.6%)
College Graduate	1 (4.8%)
Advanced Degree	10 (47.6%)
Employment Status, n (%)	
Student	7 (33.3%)
Employed	11 (52.4%)
Unemployed	3 (14.3%)

Table 3.

Self-reported ratings of pain, unpleasantness, positive emotion, and nostalgia.

	Uninterrupted Sleep		Forced Awakenings	
	Neutral	**Rewarding**	**Neutral**	**Rewarding**
Pain Intensity (0–10)	5.96 (2.18)	5.28 (2.10)	5.61 (2.04)	5.04 (1.97)
Pain Unpleasantness (0–10)	5.37 (2.36)	4.32 (2.09)	5.22 (2.56)	4.40 (2.45)
Positive Emotion (1–5)	3.73 (2.57	7.52 (2.22)	3.54 (2.76)	7.11 (2.33)
Nostalgia (1–5)	2.43 (2.82)	6.95 (2.81)	2.53 (2.99)	6.82 (2.97)

Note. Means (and standard deviations) for pain intensity ratings obtained following noxious thermal stimuli delivered in the context of neutral and rewarding music, following Uninterrupted Sleep and Forced Awakenings.

Table 4.

Whole Brain Activations and Deactivations Following Uninterrupted Sleep

Anatomical Regions	Cluster p-value*	Cluster Size (Voxels)	Side	Peak T-Value	MNI coordinates x	y	z
Pain Onset During Neutral Music Following Uninterrupted Sleep							
pINS/ S2/ aINS	<.001	4661	R	11.9	54	−2	2
				9.1	48	−8	0
				8.3	52	−12	6
		4170	L	9.0	−38	−14	2
				7.7	−50	−2	−6
				7.6	−58	−16	12
Bilateral NAc	<.001	419	R	6.2	10	6	2
				5.8	4	18	−4
			L	6.3	−16	24	−10
pMCC	.021	151	R	4.7	6	8	38
				4.5	6	8	48
				4.5	0	14	42
Tonic Pain During Neutral Music Following Uninterrupted Sleep							
pINS/ S2/ aINS	<.001	2438	R	7.3	54	10	−2
				7.3	40	4	−16
				6.9	54	−16	14
pINS/ S2	<.001	666	L	5.3	−60	−14	10
				4.8	−58	−14	2
				4.7	−58	6	4
Cerebellum	.014	240	L	5.9	−26	−72	−22
				5.5	−38	−62	−26
				3.8	−36	−52	−32
Pain Offset During Neutral Music Following Uninterrupted Sleep							
pINS/ S2	<.001	2148	R	7.0	40	−2	−8
				6.9	60	−16	14
				6.2	58	−2	6
		440	L	4.9	−64	−18	12
				4.9	−52	−16	4

Pain Offset During Neutral Music Following Uninterrupted Sleep							
Anatomical Regions	**Cluster p-value***	**Cluster Size (Voxels)**	**Side**	**Peak T-Value**	**MNI coordinates**		
					x	**y**	**z**
				4.9	−58	−10	8
IFC	.003	271	R	5.6	38	38	2
				4.4	42	44	−6
				4.3	44	48	8
aINS	<.001	149	R	5.1	36	6	12
				4.9	38	14	12

*Values are corrected for FWE.

Table 5.

Summary of Mixed Effects Analyses for Left and Right NAc by Sleep and Affective Valence

		Left NAc		Right NAc	
Task Condition	**Fixed Effects**	**F**	**p**	**F**	**p**
Pain Onset	Sleep	6.420	***0.014**	4.269	***0.043**
	Valence	1.232	0.271	3.195	0.079
	Interaction	0.005	0.946	0.025	0.874
Tonic Pain	Sleep	5.783	***0.019**	0.046	0.830
	Valence	0.002	0.963	0.007	0.934
	Interaction	0.003	0.955	0.114	0.737
Pain Offset	Sleep	0.564	0.456	0.397	0.531
	Valence	0.809	0.372	0.389	0.535
	Interaction	0.061	0.806	0.053	0.819

Table 6.

PPI Analysis for NAc Connectivity

Effect of Pain Onset During Neutral Music, Uninterrupted Sleep							
Anatomical Regions	**Cluster, Uncorrected p-value***	**Cluster, Corrected p-value***	**Cluster Size (Voxels)**	**Peak T-Value**	**MNI coordinates**		
					x	**y**	**z**
pMCC	<.001	0.004	135	7.14	4	−10	40
NAc/ VP	0.001	0.017	104	5.92	14	12	−8
aMCC	<.001	<.001	225	5.47	2	18	38
NAc/ VP/ BNST	<.001	<.001	274	5.45	−12	12	0
S2	<.001	<.001	299	5.39	60	−36	26
Putamen	0.002	.042	85	5.29	30	−20	6
Thalamus	<.001	0.003	146	5.36	−10	−14	6
	<.001	.003	144	4.79	18	−10	8

Effect of Valence During Pain Onset, Uninterrupted Sleep (Positive Music > Neutral Music)							
Anatomical Regions	**Cluster, Uncorrected p-value***	**Cluster, Corrected p-value***	**Cluster Size (Voxels)**	**Peak T-Value**	**MNI coordinates**		
					x	**y**	**z**
mOFC	0.001	0.022	90	5.18	6	30	−17

Interaction of Sleep Condition and Valence During Pain Onset (US>FA x Neutral Music>Positive Music)							
Anatomical Regions	**Cluster, Uncorrected p-value***	**Cluster, Corrected p-value***	**Cluster Size (Voxels)**	**Peak T-Value**	**MNI coordinates**		
					x	**y**	**z**
aMCC	<.001	0.010	119	4.58	−2	14	32

VP, ventral pallidum, BNST, bed nucleus of stria terminalis, S2, secondary somatosensory cortex, mOFC, medial orbitofrontal cortex, a/pMCC anterior/posterior midcingulate cortex