The rewards of music listening: Response and physiological connectivity of the mesolimbic system

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Although the neural underpinnings of music cognition have been widely studied in the last 5 years, relatively little is known about the neuroscience underlying emotional reactions that music induces in listeners. Many people spend a significant amount of time listening to music, and its emotional power is assumed but not well understood. Here, we use functional and effective connectivity analyses to show for the first time that listening to music strongly modulates activity in a network of mesolimbic structures involved in reward processing including the nucleus accumbens (NAc) and the ventral tegmental area (VTA), as well as the hypothalamus and insula, which are thought to be involved in regulating autonomic and physiological responses to rewarding and emotional stimuli. Responses in the NAc and the VTA were strongly correlated pointing to an association between dopamine release and NAc response to music. Responses in the NAc and the hypothalamus were also strongly correlated across subjects, suggesting a mechanism by which listening to pleasant music evokes physiological reactions. Effective connectivity confirmed these findings, and showed significant VTA-mediated interaction of the NAc with the hypothalamus, insula, and orbitofrontal cortex. The enhanced functional and effective connectivity between brain regions mediating reward, autonomic, and cognitive processing provides insight into understanding why listening to music is one of the most rewarding and pleasurable human experiences.
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Introduction

Music is an important part of most people's lives. Based on the archeological record, music has been with our species for a very long time—as long as anything else for which we have evidence (Cross, 2001). Its ubiquity and its antiquity demonstrate its importance to us: no known culture now or in the past lacks music (Huron, 2001; Sloboda and Juslin, 2001). Mothers in every known culture sing songs to their infants, making music one of the newborn's first experiences (Trehub, 2003).

Music represents a dynamic form of emotion (Dowling and Harwood, 1986; Helmholtz, 1863/1954; Langer, 1951), and the conveying of emotion is considered to be the essence of music (Meyer, 1956; Nietzsche, 1871/1993) and the reason that most people report spending large amounts of time listening to music (Juslin and Sloboda, 2001). Somewhat paradoxically, the cognitive and structural aspects of music have been the most extensively studied, perhaps because methods for studying them have been part of the standard cognitive psychology paradigms for decades. Advances in affective neuroscience as well as new links between neurochemistry and cognition have only recently made it possible to study emotion in music rigorously (Blood and Zatorre, 2001; Blood et al., 1999; Panksepp, 2003).

Historically, studies in affective neuroscience have focused almost exclusively on the processing of negative emotions (LeDoux, 2000). The few extant studies of positive emotion have tended to use drugs of addiction to induce those positive emotions artificially (Berridge, 2003), and only recently have more naturalistic and ecologically valid studies of positive emotion been conducted (Kringelbach et al., 2003; Small et al., 2001). Listening to classical music is known to evoke strong emotions, including feelings of pleasure (Krumhansl, 1997; Sloboda and Juslin, 2001). Further, this experience is often accompanied by physical responses (Panksepp, 1995), such as thrills, chills, shivers, and changes in heart rate that can be blocked by nalaxone, a known opioid antagonist (Goldstein, 1980). Opioid transmission in the NAc has been associated with dopamine release in the ventral tegmental area (VTA) (Kelley and Berridge, 2002), and together they are involved in mediating the brain's responses to reward. If one could show the involvement of these systems in music processing, it would illuminate the

underlying neural basis of subjective reports that music listening is rewarding.

Relatively little is currently known about the neural bases of these responses as most brain imaging studies of music have focused on its acoustic and cognitive aspects (Zatorre and Peretz, 2001). However, research in many different domains of basic and clinical neuroscience has shown that the nucleus accumbens (NAc) is one of the prominent brain areas involved in processing rewarding and pleasure-evoking stimuli (Breiter et al., 2001; Knutson et al., 2001). The involvement of the NAc, VTA, and other related structures in music is poorly understood. In two PET studies involving musicians, Blood et al. (Blood and Zatorre, 2001; Blood et al., 1999) found that as intensity of physiological and psychological responses increased, cerebral blood flow increases and decreases were observed in brain regions thought to be involved in reward/ motivation, emotion, and arousal, including ventral striatum, mid-brain, amygdala, orbitofrontal cortex (OFC), and ventral medial prefrontal cortex. Because these studies used only musicians, the generality of these findings is not clear. The relatively poor resolution of PET prevented these investigators from definitely concluding that the NAc was activated. Here, we take advantage of the higher resolution afforded by fMRI to examine whether the NAc and other brain areas implicated in reward processing, such as the VTA are activated during music processing. More importantly, we combined fMRI with functional and effective connectivity (Friston et al., 1997; Lee et al., 2003) to further characterize and more directly probe the dynamics of brain networks involved in the affective aspects of music. This multileveled approach allows us to make inferences about the underlying functional connectivity and neurochemistry based on the pattern of activations.

Functional connectivity refers to the association or dependency of activation between regions. One way to examine functional connectivity is to use temporal correlations between spatially remote neurophysiological events. This represents a "model free" characterization of brain connectivity (Lee et al., 2003). A second, potentially more powerful method, uses effective connectivity to measure the interaction of one brain region with another, mediated by anatomical connections between them as opposed to the direct effect of task or activation in a common driving region (Friston et al., 1997). We applied methods for analysis of both functional and effective connectivity to the same data; we intended that the relatively model-free results of correlational analysis could sub-stantiate and corroborate the anatomically modeled results of the effective connectivity analysis (Honey et al., 2003).

We examined brain responses to classical music using high-resolution functional magnetic resonance imaging (fMRI) at 3 T. Thirteen right-handed non-musicians participated in the study. We used non-musicians in our study to ensure that our results are uncontaminated by any schemas that expert musicians may have had for musical processing. Digitized sound files were taken from compact disc recordings of standard pieces in the classical repertoire (such as Beethoven's *Fifth Symphony* and Mozart's *Eine Kleine Nachtmusik*; the complete stimulus list may be found in Levitin and Menon, 2003, see also http://www.psych.mcgill.ca/ labs/levitin/research/musicsamples.html). As a control, scrambled versions were created by concatenating 250–350 ms random excerpts. This yielded stimuli that retained the pitch, loudness, and timbre of the corresponding piece of music, but lacked any predictable musical structure. The data set used in this report is the same as the one used in an earlier report in which we focused on the lateral inferior frontal cortex (Levitin and Menon, 2003). In

contrast to our previous study, the focus here is on examining brain response and connectivity related to the affective aspects of music listening. Specifically, we focus on modeling brain interactions mediated by the mesolimbic dopaminergic reward system.

We hypothesized that the NAc would be strongly activated when subjects listened to classical music, and, furthermore, that NAc response would be correlated with activation in the hypothalamus, a brain region that is known to control autonomic and physiological response to emotional stimuli. Based on studies in animals which have highlighted the vital role of interaction between NAc and VTA in reward processing (Schultz, 2002), we also examined the functional and effective connectivity of these regions.

Materials and methods

Subjects

Thirteen right-handed and normal-hearing subjects participated in the experiment; age ranged from 19.4–23.6 years, 7 females and 6 males. Subjects were non-musicians, that is, they had never learned singing or an instrument, and they did not have any special musical education besides what is normally given in public schools (Maess et al., 2001). The participants gave informed consent prior to the experiment, and the protocol was approved by the Stanford University School of Medicine Human Subjects Committee.

Stimuli

The stimuli for the music conditions consisted of digitized sound files (22,050 sampling rate, 16 bit mono) presented in a random order taken from compact disc recordings of standard pieces in the classical repertoire. The first 23 s of the pieces were used. Scrambled versions were created by randomly drawing 250–350 ms variable-sized excerpts from each piece and concatenating them with a 30 ms linear cross-fade between excerpts. The differences between the control and the experimental conditions were as follows. Both retain, over the course of the 23 s excerpt, the same distribution of pitch and loudness (this must logically be true, since elements were simply reordered) and the same spectral information. Fast Fourier transforms (FFTs) between the normal and scrambled versions correlated significantly, Pearson's $r = 0.99$, $P < 0.001$ for all selections. What is different between the two versions is that the scrambled music utterly lacks temporal structure—what is some-times referred to as temporal coherence (Deutsch, 1999) or temporally driven expectations (Levitin and Menon, 2003). In the scrambled version, those elements that manifest themselves across time are disrupted, such as melodic contour, the navigation through tonal and key spaces (Janata et al., 2002), and any rhythmic groupings lasting longer than 350 ms. Other details of the stimuli used in this study may be found in Levitin and Menon, 2003.

Subjects listened to the sounds at a comfortable listening level over headphones employing custom-built, magnet compatible pneumatic audio delivery system. Pilot testing with a separate group of six participants established that the stimuli were equally matched for loudness.

Pleasantness ratings

Six subjects participated (1 male, 5 females) in the pilot study. Subjects were drawn from the same population as subjects in the

neuroimaging experiment. We used a separate set of subjects because we did not want subjects in the scanner to be explicitly thinking about, or making decisions, about the emotional content of the songs, which might have contaminated our neuroimaging results. If a subject coded something as "pleasant" during the scan, we would not know whether the neural activations observed were a "second order effect" of the subject having labeled it pleasant, or whether they were primary effects of the actual experience of pleasantness. Moreover, to ask the subjects to make ratings after the scan session would force us to rely on the subjects' memory of what they might have been feeling during the scan. We did not want to rely on memory for the stimuli because of the distortions associated with recall.

Each subject gave a rating to the stimuli, in both its scrambled and unscrambled version, used in this study. The rating scale ran from 1 (not at all pleasant) to 7 (very pleasant) and the midpoint was labeled "neither pleasant nor unpleasant." Ten pieces were used, resulting in a pool of 20 excerpts which were presented in a randomized order. Overall, the mean scores for normal (6.13 ± 0.76) and scrambled (2.35 ± 1.12) stimuli were significantly different ($t(59) = 23.482; P < 0.001$). A piece-by-piece analysis also showed similarly significant differences between each normal/scrambled piece pair.

Experiment

Music and scrambled music pieces were presented in alternating 24-s experimental and control epochs using a standard fMRI block-design. The order of the epochs was randomized across subjects. In each epoch, music/scrambled stimuli were presented for 23 s, followed by a 1 s interstimulus interval.

fMRI acquisition

Images were acquired on a 3 T GE Signa scanner using a standard GE whole head coil (software Lx 8.3). Images were acquired every 2 s in a single run that lasted 8 min and 48 s. A custom-built head holder was used to prevent head movement. 28 axial slices (4.0 mm thick, 0.5 mm skip) parallel to the AC–PC line and covering the whole brain were imaged with a temporal resolution of 2 s using a T2* weighted gradient echo spiral pulse sequence (TR = 2000 ms, TE = 30 ms, flip angle = 70°, 180 time frames, and 1 interleave) (Glover and Lai, 1998). The field of view was 200×200 mm, and the matrix size was 64×64, providing an in-plane spatial resolution of 3.125 mm. To reduce blurring and signal loss arising from field inhomogeneities, an automated high-order shimming method based on spiral acquisitions was used before acquiring functional MRI scans (Kim et al., 2002). To aid in localization of functional data, a high resolution (acquired resolution = $1.5 \times 0.9 \times 1.1$ mm) T1-weighted spoiled grass gradient recalled (SPGR) inversion recovery 3D MRI sequence was also acquired in the same scanning session.

Stimulus presentation

The task was programmed using Psyscope on a Macintosh (Cupertino, CA) computer. Auditory stimuli were presented binaurally using a custom-built magnet compatible system that attenuated scanner sound by approximately 28 dB. The loudness levels at the head of the participant due to the fMRI equipment during scanning were approximately 98 dB (A), and so after the attenuation provided by the ear inserts, background noise was approximately 70 dB (A) at the ears of the listener. The experimenters set the stimuli at a comfortable listening level determined individually by each participant during a test scan.

Image preprocessing

fMRI data were pre-processed using SPM99 (http://www.fil.ion.ucl.ac.uk/spm). Images were corrected for movement using least squares minimization without higher-order corrections for spin history (Friston et al., 1996), and were normalized to stereotaxic Talairach coordinates using non-linear transformations (Ashburner and Friston, 1999). Images were then resampled every 2 mm using sinc interpolation and smoothed with a 4 mm Gaussian kernel to reduce spatial noise.

Statistical analysis

Statistical analysis was performed using the general linear model and the theory of Gaussian random fields as implemented in SPM99. MNI coordinates were transformed to Talairach coordinates using a non-linear transformation (Brett et al., 2002). Activation foci were superimposed on high-resolution T1-weighted images and their locations were interpreted using known neuroanatomical landmarks (Duvernoy, 1995; Duvernoy et al., 1999) and cross-validated with the brain atlas of Mai et al. (2004).

A within-subjects procedure was used to model all the effects of interest for each subject. Confounding effects of fluctuations in global mean were removed by proportional scaling where, for each time point, each voxel was scaled by the global mean at that time point. Low-frequency noise was removed with a high pass filter (0.5 cycles/min) applied to the fMRI time series at each voxel. The design matrix used in the general linear model analysis consisted of the regressors corresponding to the music stimuli, scrambled music stimuli, the global mean as described above, and a constant term. We then defined two effects of interest for each subject using the following contrasts of the regression parameter estimates—music *minus* scrambled music and scrambled music *minus* music. Group analysis was performed using a random-effects model that incorporated a two-stage hierarchical procedure. This model estimates the error variance for each condition of interest across subjects, rather than across scans and therefore provides a stronger generalization to the population from which data are acquired (Holmes and Friston, 1998). In the first stage, contrast images for each subject and each effect of interest were generated as described above. In the second stage, these contrast images were analyzed using a general linear model to determine voxel-wise *t* statistics. One contrast image was generated per subject, for each effect of interest. Finally, the *t* statistics were normalized to *Z* scores, and significant clusters of activation were determined at the cluster level ($P < 0.01$), with whole-brain corrections for multiple comparisons (Poline et al., 1997).

Functional connectivity analysis

Functional connectivity analyses were conducted by computing the correlation between activation in specific regions of interest. Individual time series were extracted from the NAc, VTA, and hypothalamus voxels within a 4-mm radius of the local activation maxima in each of these regions. For each subject, fMRI time series (one for each ROI and subject) were averaged separately across voxels within these ROIs after high-pass filtering ($f < 1/120$

Hz) the low-frequency drift. Pairwise, Pearson correlation coefficients were computed between the resulting time series, separately for the music and scrambled music conditions. The correlation coefficients between regions i and j, $r_{i,j}$, were transformed to a normal distribution using Fisher's r-to-z transformation: $z_{i,j} = 0.5 * \ln((1 + r_{i,j})/(1 - r_{i,j}))$. Task-related changes in functional connectivity were then examined by comparing the resulting Z scores against the null hypothesis of $r_{i,j} = 0$ (Honey et al., 2003).

Effective connectivity analysis

This analysis reflects a more elaborate examination of the interaction of multiple brain regions. It models and attempts to remove the potential effects of confounding influences, such as a common driving input, mediating the interaction between specific brain regions. Effective connectivity is defined here as the influence of one region upon another, after discounting the influence of task-related effects as well as the effects of a common driving input (Friston et al., 1997). Effective connectivity is modeled here as a physio-physiological interaction (PPI), in which the modulatory effects of the VTA-NAc dopaminergic pathway are examined. The precise model used in our study is schematically illustrated in Fig. 1, it seeks to determine which brain areas show significant VTA-mediated interaction with the NAc.

The individual time series for the NAc and VTA were obtained by extracting the raw voxel time series in a sphere (4-mm radius) centered on the coordinates of the peaks in the group activation maps. These time series were mean-corrected and high-pass filtered ($f < 1/120$) to remove low-frequency signal drifts. No other transforms were performed on the time series. Once these time series were obtained for each subject, the interaction term (referred to as "PPI regressor") was computed as the vector resulting from the element-by-element product of the mean corrected NAc and VTA time series. In addition to the PPI regressor, the design matrix included the main effects of task as
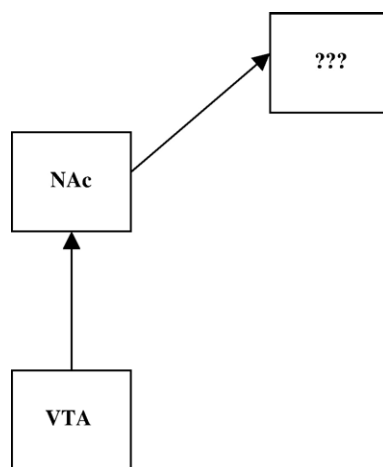

Fig. 1. Schematic model of the physiological interactions examined with effective connectivity analysis. The circuit examines the modulatory effect of the VTA–NAc pathway, a key component of the mesolimbic dopaminergic reward system. In this model, dopamine release in the VTA influences NAc responses and coactivation of this critical reward processing pathway further modulates brain responses to music. The effective connectivity analysis conducted in our study examines precisely which brain regions (indicated with the question marks) show such responses.

described above and the mean-corrected time series from the NAc and VTA voxels of interest. The latter three covariates remove common driving effects from other brain regions to the fullest extent possible, within the constraints of the neural network model under consideration. Altogether, our analysis of effective connectivity was thus specific for VTA-modulated NAc influences that occurred over and above any task and context-independent effects.

Brain regions that showed significant PPI effects were determined by testing for positive slopes of the PPI regressor, i.e., by applying a t contrast that was 1 for the PPI regressor and 0 for all other effects. Similarly, brain regions showing negative PPI effects were determined by testing for negative slopes of the PPI regressor. Subject-specific contrast images were determined and then entered into random effects group analyses. This second level connectivity analysis allowed us to extend the inference to the population from which the data were acquired. The significance of the results was assessed at the cluster-level ($P < 0.01$), with whole-brain corrections for multiple comparisons.

Results

Brain activation to music

As hypothesized, significant activation was observed in several subcortical regions including the NAc, VTA, and the hypothalamus (Fig. 2). In addition, significant bilateral activation was observed in cortical regions, including the left and right inferior frontal cortex (IFC), left OFC, anterior cingulate cortex, and also the cerebellar vermis and brainstem (Fig. S1 and Table S1 in Appendix A). Activation of all regions, except the VTA, was detected using a conservation threshold of $P < 0.01$, corrected for multiple comparisons. VTA activations were detected using a lower threshold of $P < 0.05$, corrected for multiple comparisons (Fig. 2B).

Functional connectivity analysis

Based on the activations noted above, we identified peaks within the NAc (MNI coordinates: $-4, 6, -4$ mm; t score = 3.85), VTA ($2, -12, -12$ mm; t score = 2.58), and the hypothalamus ($-4, -4, -4$ mm; t score = 2.68). The peak within the NAc was clearly separated from the caudate dorsally and from the bed nucleus of the stria terminalis. The VTA activation could be clearly identified as focal activation in a region medial to the substantia nigra pars compacta and the hypothalamic activation could be clearly identified inferior to the thalamus, separated from the hypothalamic sulcus and adjoining the third ventricle.

Time series analysis showed that correlations between ongoing activity in the NAc and VTA (Fig. 3) across subjects were significantly greater than zero ($r = 0.18 \pm 0.05$; $t(df = 12) = 3.09$; $P < 0.01$). NAc and hypothalamus time series showed significantly higher correlation (0.36 ± 0.07; $t(12) = 4.76$; $P < 0.001$). Similarly, hypothalmaus and VTA time series showed significantly higher correlation ($r = 0.23 \pm 0.06$; $t(12) = 3.60$; $P < 0.005$). These results suggest a tight coupling between the NAc, VTA, and the hypothalamus during music processing.

Effective connectivity analysis

Effective connectivity analysis examined VTA-mediated interactions of the NAc, after discounting the effects of a common
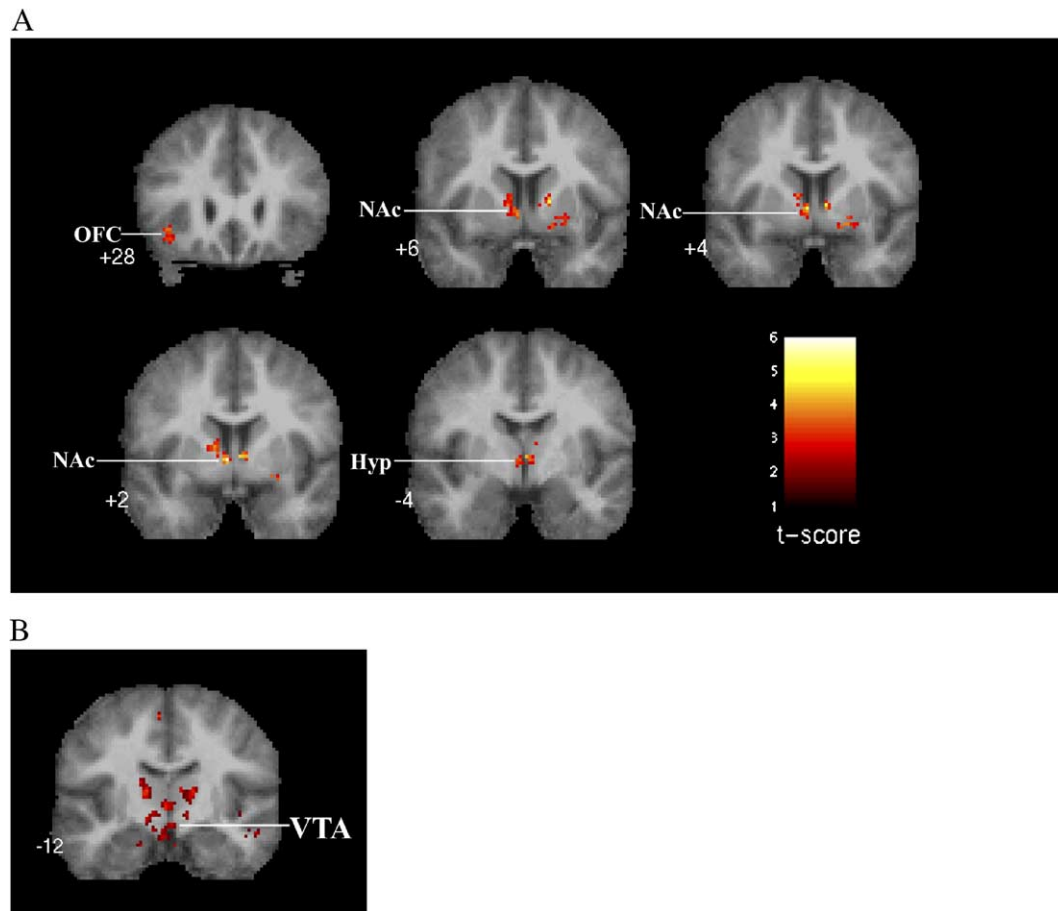
Fig. 2. Task-related group activation during music, compared to scrambled music. Activation of the nucleus accumbens (NAc) and a network of related mesolimbic structures including the ventral tegmental area (VTA), the hypothalamus, and orbitofrontal cortex (OFC) are shown. (A) All activations were significant at $P < 0.01$, corrected for multiple comparisons, except (B) the VTA, a difficult to image structure, which was significant at $P < 0.05$ (corrected). The NAc is located immediately lateral to the base of the septum pellucidum, the hypothalamus adjoins the third ventricle, and the VTA is located medial to the substantia nigra, pars compacta. The Talairach coordinates (in mm) of each section are shown at the bottom left of each panel. Activation is shown superposed on group-averaged high-resolution structural images.
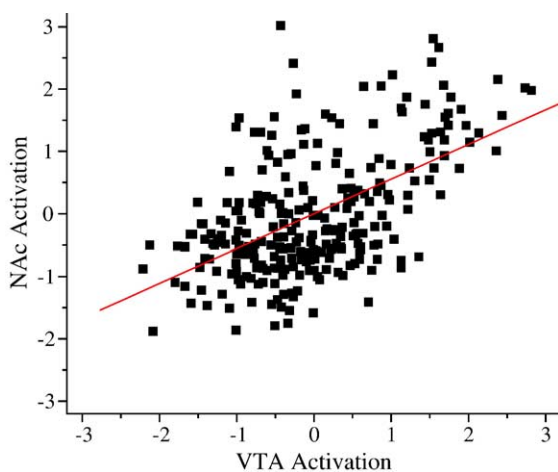

Fig. 3. Representative measurements from a single subject showing the tight correlation between fMRI responses in the NAc and VTA. The figure is a scatter plot of fMRI signals extracted from the NAc and VTA at various time points; each individual point in the figure represents signal level in the two regions at a single time point. In this subject, as in most subjects, the correlation was highly significant ($P < 0.001$). Time series in each region were mean-corrected and normalized by the standard deviation.

driving input and other confounding factors (Fig. 4). Significant VTA-mediated interactions of the NAc were observed with the hypothalamus, left anterior insula, left mid-to-posterior insula, as well as the left and right OFC, left IFC, and the right middle and superior temporal gyri (Fig. 5, Table 1). A more complete view of these activations is shown in Fig. S2 in Appendix A. Representative single-subject measurements, illustrating VTA-mediated inter-actions of the NAc with the hypothalamus and the insula, are shown in Fig. 5. These results provide evidence for robust VTA-dependent NAc interactions with the hypothalamus, insula, and OFC.

Interestingly, no brain regions showed negative VTA-mediated interactions with the NAc.

Discussion

We examined the reward and affective components of music listening using fMRI. Our findings can be grouped into three major categories. The pattern of activations informs the functional neuroanatomy of music listening. The connectivity analyses (both effective and functional) inform network and system function, and an interaction among affective and autonomic systems in the brain.
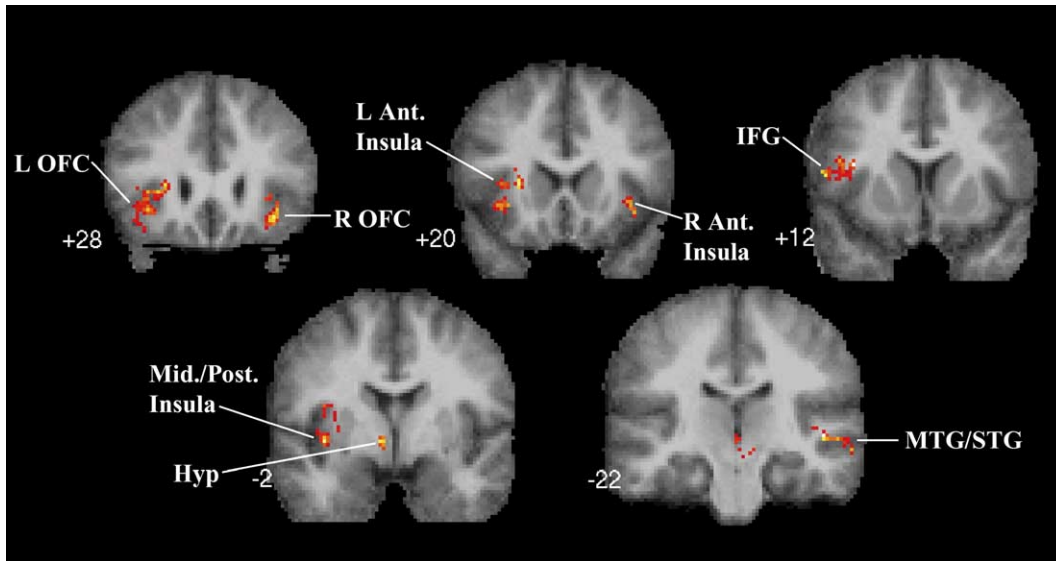
Fig. 4. Brain regions that showed significant VTA-mediated interactions with the NAc (P < 0.01, corrected). Prominent among these regions are the hypothalamus, anterior insula, and the orbitofrontal cortex (OFC), bilaterally, and the left mid-to-posterior insula, all brain regions known to be involved in modulating physiologic and affective responses to emotional and rewarding stimuli.
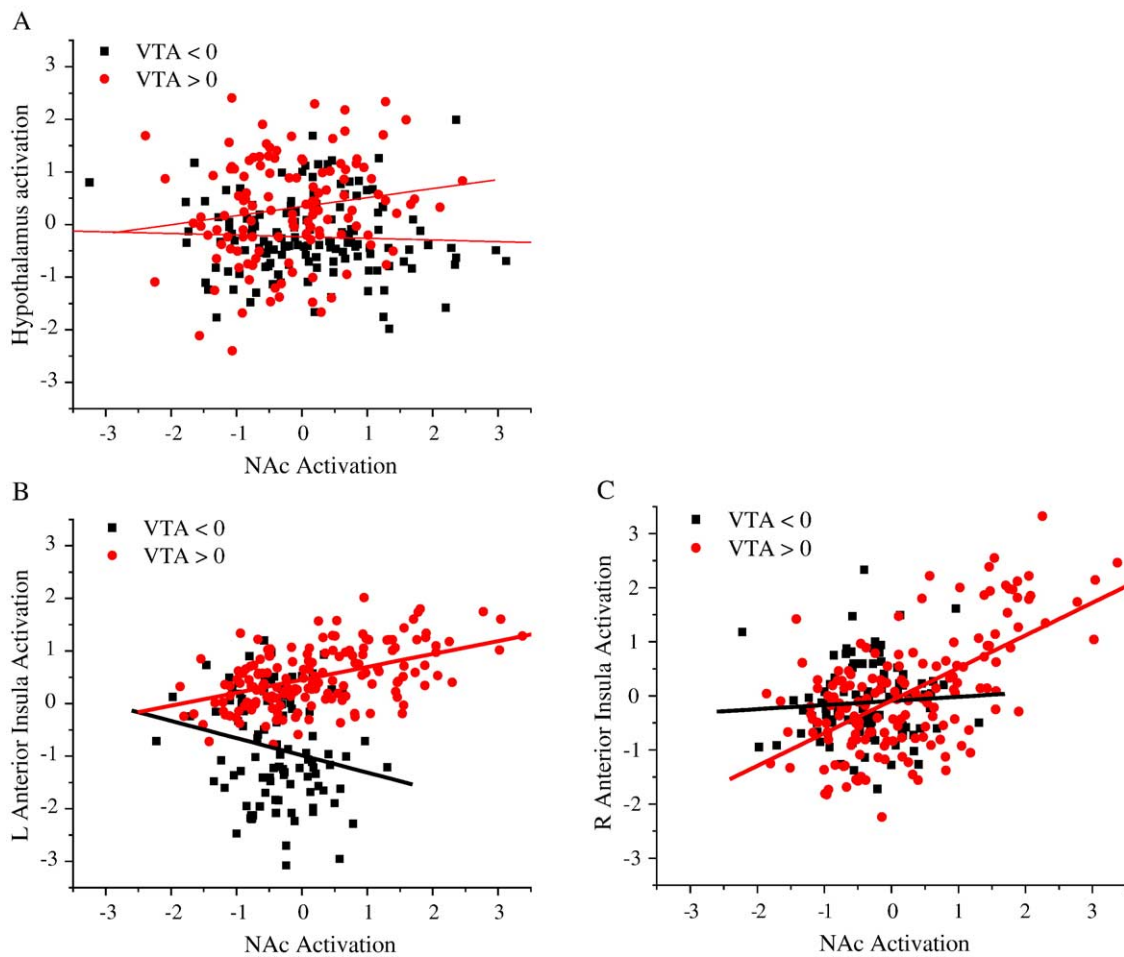

Fig. 5. VTA-mediated interactions of the NAc with the (A) hypothalamus (peak at −8, −2, −4 mm) (B) left anterior insula (peak at −30, 30, 2 mm) and (C) right anterior insula (peak at −56, 10, 10 mm). For illustrative purposes, data were categorized based on the level of VTA response. Measurements during positive (>0) VTA responses are shown in red and negative (<0) VTA responses are shown in black. In all three regions, the mean-corrected and normalized activity is shown as a function of the mean-corrected and normalized NAc activity. Regression slopes were significantly greater during the VTA > 0 condition for all three regions.

Table 1
VTA-mediated effective connectivity of the NAc

Brain regions	Cluster P value (corrected)	# of voxels	Maximum Z score	Peak Talairach coordinates (mm)
Left and right hypothalamus and substantia nigra	0.001	127	4.22	6, −14, −10
Left inferior frontal cortex (BA 47), anterior insula/orbitofrontal cortex (BA 11)	<0.001	430	4.21	−56, 10, 10
Right middle temporal gyrus	0.017	88	3.95	50, −22, 0
Left mid-to-posterior insula	0.004	108	3.77	−40, −2, −4
Right anterior insula/orbitofrontal cortex (BA 11)	<0.001	145	3.62	36, 28, −12

Brain areas that showed significantly greater VTA-mediated interaction with the NAc ($P < 0.01$, corrected for multiple comparisons).

Thirdly, these analyses also allow us to make informed speculations about neurochemical processes, in particular dopaminergic pathways, mediating affective responses to music. For a discussion of the perceptual and cognitive aspects of temporal information processing in music, we refer the reader to Levitin and Menon (2003).

Neuroanatomy

We found that passive listening to music resulted in significant activation of a network of subcortical structures including the NAc, the VTA, and the hypothalamus. In a related positron emission tomography (PET) study, activation in the ventral striatum was correlated with the intensity of pleasurable responses to music (Blood and Zatorre, 2001), but PET lacks the spatial resolution to image the NAc and consequently no focal activation has previously been reported there. Using PET, Brown et al. (2004) reported activation in the NAc in response to passive listening to unfamiliar but pleasant music. Our study corroborates these findings, as well as earlier findings of Blood et al., and importantly takes advantage of the better spatial resolution of fMRI to more concretely address the issue of NAc activation (Brown et al., 2004). Our results extend Blood et al.'s (Blood and Zatorre, 2001) finding by demonstrating for the first time the involvement of the NAc itself. Previous studies of the NAc in humans have focused on its role in processing explicit and tangible incentives, such as monetary reward (Knutson et al., 2001) and recreational and addictive drugs (Breiter et al., 1997; Robinson and Berridge, 2003). Our results show that the NAc is invoked even when no explicit reward is present, as is the case with music, as noted here, and humor, as noted in a previous study (Mobbs et al., 2003).

Significant activation was also detected in the hypothalamus, a brain region that modulates autonomic responses, including heart rate and respiration. The pleasurable experience of listening to music is often accompanied by changes in these autonomic responses (Blood and Zatorre, 2001; Goldstein, 1980; Krumhansl, 1997), giving rise to subjective reports of "thrills" (Goldstein, 1980) and "chills" (Blood and Zatorre, 2001). To our knowledge, this is also the first direct evidence of hypothalamic response to music.

The specific contrasts used in this study, comparing normal and scrambled stimuli, do not allow us to conclusively determine whether activation in the VTA and NAc is due to significantly increased response during music vs. the resting state or if the effect is driven by a decrease in activity in these areas during the unpleasant scrambled stimuli. Thus, the results cannot really be attributed to listening to pleasant music per se, but rather to listening to pleasant music vs. listening to unpleasant musical

sounds. However, subjects found the 23 s of normal music as a pleasant and rewarding stimulus compared to a similar duration of scrambled music which subjects rated slightly better than "not at all pleasant". Newer experiments with a passive rest condition (see also Brown et al., 2004) indicate that the relative activation of the limbic structures arising from the two classes of stimuli is due to increased activation in response to music as opposed to deactivation to scrambled music stimuli.

It should be noted that relatively superficial features of music are known to drive the affective response. In particular, tempo and pitch range account for a large proportion of the variance in people's judgments of happy vs. sad music. In addition, other pitch variables (including interval size, contour) and loudness influence distinct dimensions of affect such as valence, energy, and tension (Thompson et al., 2001). We intentionally chose excerpts that were relatively homegenous along some of the salient dimensions: all pieces had a moderate tempo, were in major keys, and were presented at a similarly comfortable loudness level. Had we used a broader spectrum of music – including minor key pieces, very slow and very fast pieces – we hypothesize that similar experience of reward would have obtained while invoking different underlying mood and arousal reactions; this is because people generally find music rewarding regardless of whether it is marked as "sad" or "happy" (Sloboda and Juslin, 2001).

Network and system function

Connectivity analyses allowed us to detect associations between neural regions in music processing that conventional activation-based analysis cannot address. It permitted an examination of the moment-to-moment fluctuations in neural systems induced by the musical stimuli. Functional connectivity analysis showed that responses in the NAc and VTA were highly correlated as were responses between the NAc and the hypothalamus. This suggests that tightly coupled interactions in a tripartite network involving the NAc, VTA, and hypothalamus may serve to mediate brain responses to the reward and affective aspects of music.

To further elucidate these findings, we used effective connectivity analysis to examine network interactions, without the confounding effects of a common driving input. Specifically, we examined the role of the mesolimbic dopaminergic pathway involving the NAc and the VTA. The analysis tests for brain regions that are co-activated with the NAc only at those specific points in time when the VTA is also active. In other words, we sought to find neural regions whose signal changes were time-locked with significant changes in both NAc and VTA, as a means by which to draw inferences about network function involving the dopaminergic reward pathway.

An important novel finding of our study is the strong effective connectivity between several spatially distinct brain regions associated with reward and affect. We found significant dynamic VTA-mediated interactions between the NAc and hypothalamus, insula, and the OFC. Interestingly, interactions with the OFC and IFC were more extensive than the static pattern of brain activation revealed by conventional activation-based analysis (see Figs. 2 and 5). These co-activations may have a neurochemical basis, a question which we address below.

A second aspect of our connectivity analysis pertains to interaction of the affective and autonomic systems. In addition to the hypothalamus, the insula showed extensive effective connectivity with the NAc. These structures are two of the most important nodal points in neural pathways involved with autonomic, somatic, and emotional functions (Craig, 2002, 2003). The tight ways in which the reward and affective systems appear to interact with the cognitive and autonomic systems in response to music listening are a key contribution of this study.

Possible neurochemical mechanisms

A remarkable aspect of our findings relates to detection of significant activation of the VTA. The VTA is the site of mesolimbic dopamine neuron cell bodies that project to the NAc, and dopamine release by the VTA is known to be crucial for reward processing (Berridge and Robinson, 2003). Further, we found that NAc and VTA activations were significantly correlated, suggesting an association between dopamine release and NAc response to pleasant music. It is well known that many aspects of reward processing depend on this mesolimbic pathway (Yun et al., 2004). For example, research has shown that increases in dopamine levels in the VTA and NAc are a key factor in the reinforcing effects of multiple addictive drugs (Robinson and Berridge, 2003). More commonly, natural rewards such as food and water also cause the release of dopamine in the NAc and the VTA (Kelley and Berridge, 2002). It is likely that the rewarding and reinforcing aspects of listening to music are mediated by increased dopamine levels in the VTA and the NAc. Furthermore, the hedonic aspect of reward is thought to be modulated by endogenous opioid peptide transmission within the NAc, which in turn, is known to be regulated by dopaminergic input from the VTA (Kelley and Berridge, 2002). Consistent with this, musical pleasure can be blocked by naloxone (Goldstein, 1980), a known opioid antagonist. However, it remains to be investigated whether dopamine truly facilitates the "liking", as opposed to the "wanting" reactions to hedonic impact of music (Berridge and Robinson, 2003). Our data are also consistent with neuropsychological theories which have proposed that positive affect is associated with increased brain dopamine levels (Ashby et al., 1999). Music is clearly a means for increasing positive affect.

The strong interactions between the mesolimbic reward network (NAc and VTA) and distinct frontal regions (OFC as well as the IFC) lead us to propose a tight link between the "affective" and "cognitive" sub-systems involved in music listening. Interactions with the OFC, in particular, may be related to the cognitive reward and valence representation as well as emotional control (Bechara et al., 2000). Conversely, bidirectional interactions between the OFC to the autonomic and primary reward processing areas, such as the NAc, may also influence emotional expression to the musical stimuli (Barbas et al., 2003). The directionality and timing of such interactions remain to be investigated. We also noted right MTG/

STG connectivity with the NAc, which we attribute to the reward aspect of recognizing highly schematized tonal structures (Janata et al., 2002; Tillmann et al., 2003; Zatorre et al., 1994).

There is currently some controversy over what psychophysiological constructs are mediated by opioid and dopamine transmission in these areas. Although a majority of studies have focused on reward and pleasure (Berridge, 2003; Berridge and Robinson, 2003), these regions have also been shown to be activated by noxious stimuli, including pain (Becerra et al., 2001; Horvitz, 2000). The available evidence suggests that pleasure and pain anchor opposite ends of a continuum (Becerra et al., 2001). It would be reasonable to assume that VTA-NAc responses are related to suppression of aversive stimuli (Taylor et al., 2003), which would be of a "rewarding" nature.

Taken together, our data suggest that dynamic interactions between the NAc, the VTA, and the hypothalamus may play an important role in regulating emotional responses to music. In fact, neuroanatomical studies have provided extensive evidence for direct connections between all three structures (Zahm, 2000). In conclusion, our findings shed new light on understanding the neurochemical and neuroanatomical basis for why music has an incredible power to move us, and for why listening to music is one of the most rewarding and pleasurable human experiences.

These findings are likely to have broad implications for understanding the psychological and physiological benefits of listening to music. We propose that music offers a simple and elegant way to probe the neural basis of anhedonia (the loss of pleasure in daily activities) in a number of psychiatric disorders, including depression, schizophrenia, and bipolar disorder. Musical stimuli such as those used in the present study could be used to probe the integrity of the mesolimbic reward system and to examine whether deficits in these regions are correlated with clinical symptoms. For example, depression is often accompanied by a lack of interest in pleasurable stimuli. Music can be used to investigate whether there is diminished response in these subjects in the NAc, the VTA, the insula, hypothalamus, and the orbitofrontal cortex, key brain regions involved in affect processing.

Appendix A. Supplementary data

Supplementary data associated with this article, can be found in the online version, at doi:10.1016/j.neuroimage.2005.05.053.

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